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(54) Peptides having endothelin antagonist activity, a process for preparation thereof and pharmaceutical compositions comprising the same

Peptide mit Endothelin antagonistischer Aktivität, deren Herstellung und pharmazeutische Zusammensetzungen

Peptides ayant une activité antagoniste d'endothéline, leur procédé de préparation et leurs compositions pharmaceutiques

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EP-A- 0 460 679
US-A- 4 127 534

- **BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, vol. 39, no. 8, August 1966, pages 1747-1753; H. AOYAGI et al.: "Studies of peptide antibiotics. V. Syntheses of cyclic penta- and decapeptides with the L-valyl-L-ornithyl-L-leucyl-D-phenylalanylsarcosyl sequence"**
- **BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, vol. 43, no. 4, April 1970, pages 1197-1202; S. MATSUURA et al.: "Studies of peptide antibiotics. XVI. Analogs of gramicidin S containing beta-alanine in place of L-proline"**
- **BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 156, no. 3, 15th November 1988, pages 1182-1186, Academic Press, Inc.; S. KIMURA et al.: "Structure-activity relationships of endothelin: Importance of the C-terminal moiety"**

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

EP 0 457 195 B1

Description

The present invention relates to new peptide compound and a pharmaceutically acceptable salt thereof which have endothelin antagonistic activity, to processes for its preparation, to a pharmaceutical composition comprising the same, and to a use of the same for the manufacture of a medicament for the treatment and the prevention of endothelin mediated diseases such as hypertension, and the like.

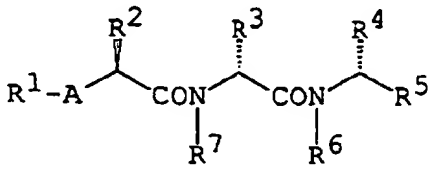
One object of the present invention is to provide new and useful peptide compound and a pharmaceutically acceptable salt thereof which have endothelin antagonistic activity.

Another object of the present invention is to provide processes for the preparation of said peptide compound and a salt thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said peptide compound or a pharmaceutically acceptable salt thereof.

Biochem. Biophys. Res. Comm. Vol. 156, No. 3, p. 1182-1186, describes the structure-activity relationship of endothelin and the importance of the C-terminal moiety.

The object compound of the present invention can be represented by the following general formula (I).



(I)

in which

R^1 is hydrogen or acyl,

R^2 is C_1-C_6 alkyl; C_6-C_{10} ar(C_1-C_6)alkyl optionally substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro and cyano; cyclo(C_1-C_6)alkyl(C_1-C_6)alkyl; or heterocyclic(C_1-C_6)alkyl optionally substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro, cyano and imino-protective group;
said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8 membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing a sulfur atom, or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

R^3 is heterocyclic(C_1-C_6)alkyl or C_6-C_{10} ar(C_1-C_6)alkyl, each of which is optionally substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro, cyano and imino-protective group,
said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 8 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing a sulfur atom, or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

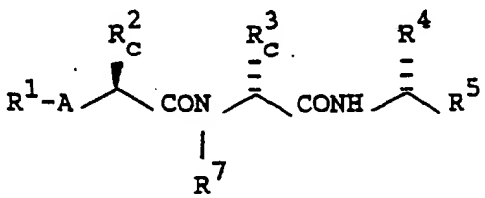
R^4 is C_1-C_6 alkyl, C_6-C_{10} ar(C_1-C_6)alkyl, amino(C_1-C_6) alkyl, protected amino(C_1-C_6)alkyl, carboxy(C_1-C_6)-alkyl, protected carboxy(C_1-C_6)alkyl or optionally substituted heterocyclic(C_1-C_6)alkyl,
said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 8 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing a sulfur atom, or
unsaturatd condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
wherein said heterocyclic group may be substituted by one or two suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro, cyano and imino-protective group,

R^5 is carboxy, protected carboxy, carboxy(C_1-C_6)-alkyl or protected carboxy(C_1-C_6)alkyl,
R^6 is hydrogen or optionally substituted C_1-C_6 alkyl,
R^7 is hydrogen or C_1-C_6 alkyl, and
A is -O-, -NH-, C_1-C_6 alkylimino or C_1-C_6 alkylene, provided that when R^3 is indol-3-ylmethyl or (N-formylindol-3-yl)methyl then R^2 is not C_3-C_5 alkyl,

or a pharmaceutically acceptable salt thereof.

Further, the compound (I) having the most potent activities can be represented by the following formula.



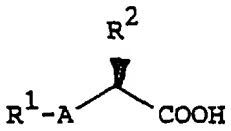
(I")

in which R^1, R^4, R^5, R^7 and A are each as defined above, and

R^2 is C_1-C_6 alkyl, and
R^3_c is indol-3-ylmethyl, N-formylindol-3-ylmethyl, N-methylindol-3-ylmethyl, N-ethylindol-3-ylmethyl, N-propylindol-3-ylmethyl or N-isobutylindol-3-yl-methyl,

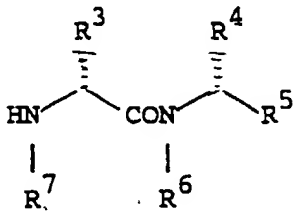
According to the present invention, the new peptide compound (I) and a salt thereof can be prepared by the processes as shown in the following schemes.

Process 1



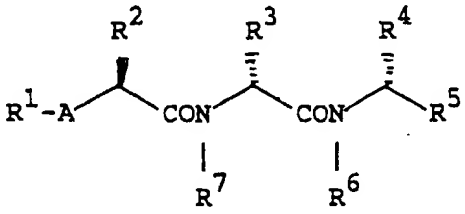
(II)

or its reactive derivative at the carboxy group, or a salt thereof



(III)

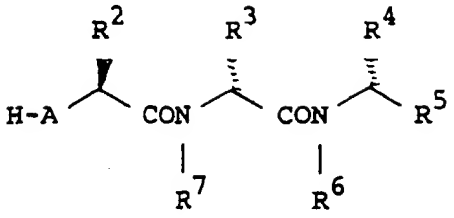
or its reactive derivative at the amino group, or a salt thereof



(I)

or a salt thereof

Process 2

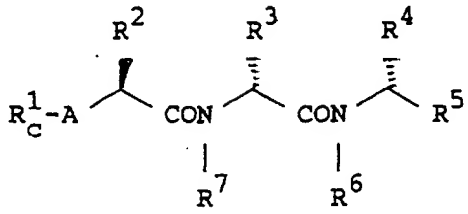


(I-a)

or its reactive derivative at the amino group, or a salt thereof

(IV)

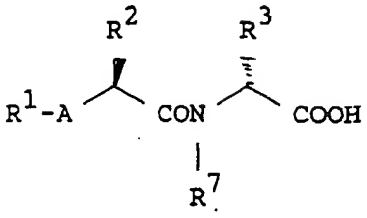
or its reactive derivative at the carboxy group, or a salt thereof



(I-b)

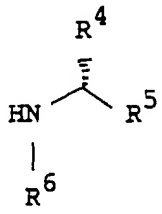
or a salt thereof

Process 3



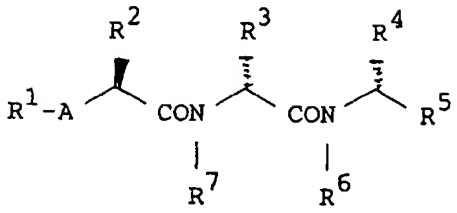
(V)

or its reactive derivative at the carboxy group, or a salt thereof



(VI)

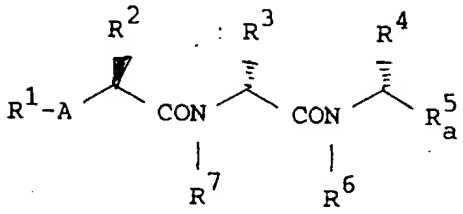
or its reactive derivative at the amino group, or a salt thereof



(I)

or a salt thereof

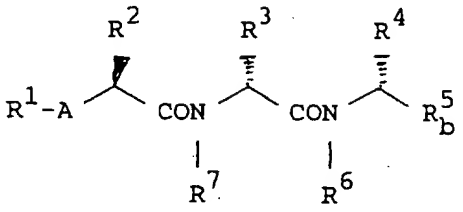
Process 4



Removal of the carboxy-protective group(s) in R_a^5 →

(I-c)

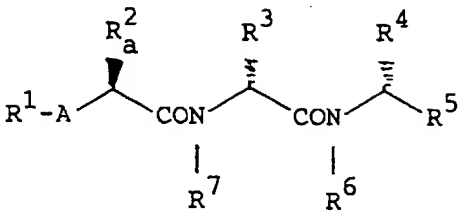
or a salt thereof



(I-d)

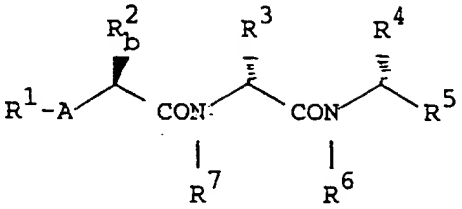
or a salt thereof

Process 5



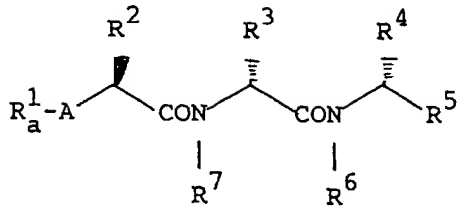
Removal of the imino-protective group in R_a^2

(I-e)
or a salt thereof



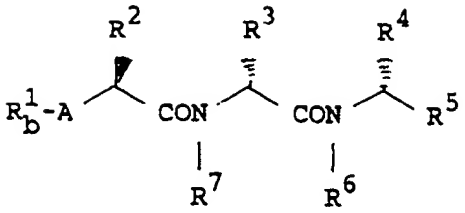
(I-f)
or a salt thereof

Process 6



Removal of the amino-protective group in R_a^1

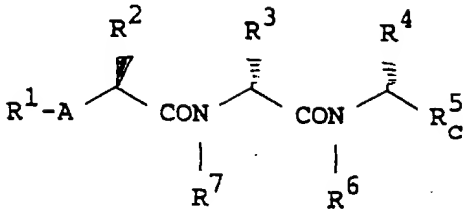
(I-g)
or a salt thereof



(I-h)

or a salt thereof

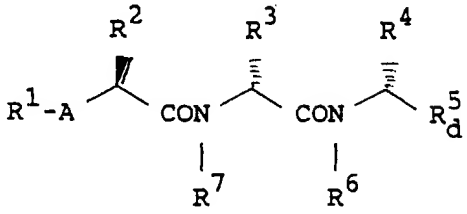
Process 7



Reaction with an optionally substituted amine, or a salt thereof

(I-i)

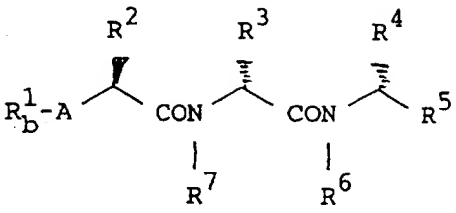
or its reactive derivative at the carboxy group, or a salt thereof



(I-j)

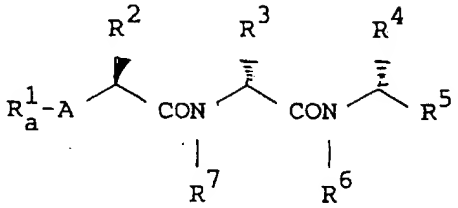
or a salt thereof

Process 8



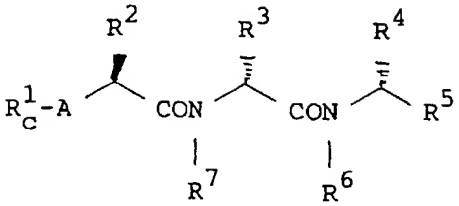
Acylation of the amino group in R_b^1

(I-h)
or a salt thereof



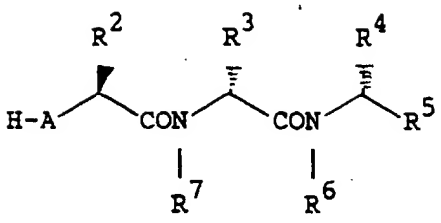
(I-g)
or a salt thereof

Process 9



Removal of the acyl group in R_c^1

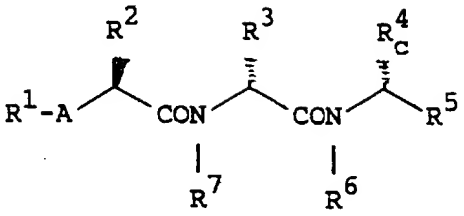
(I-b)
or a salt thereof



(I-a)

or a salt thereof

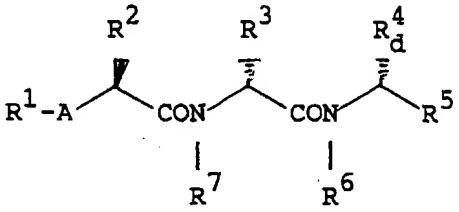
Process 10



Removal of the carboxy-protective group(s) in R^4_c →

(I-k)

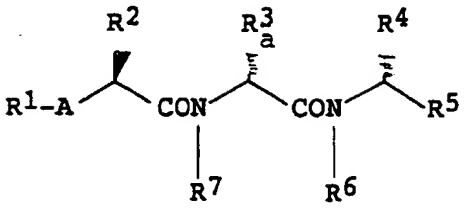
or a salt thereof



(I-ℓ)

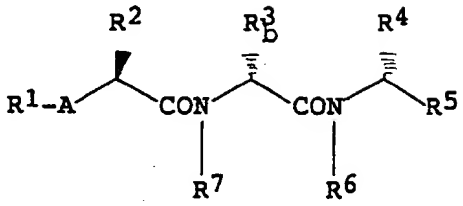
or a salt thereof

Process 11



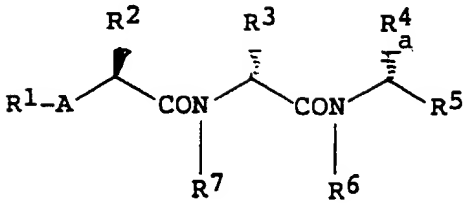
Removal of the imino-protective group(s) in R_a^3

(I-m)
or a salt thereof



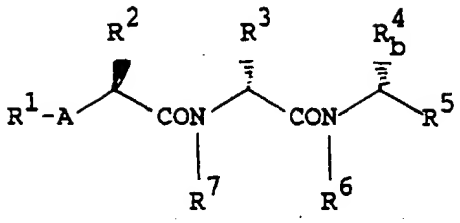
(I-n)
or a salt thereof

Process 12



Removal of the amino or imino-protective group in R_a^4

(I-o)
or a salt thereof



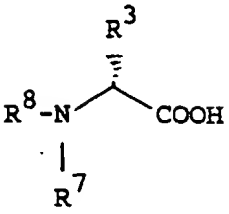
(I-p)

or a salt thereof

in which R^1, R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above,
and R^1_a, R^1_b, R^1_c, R^2_a, R^3_a, R^4_a, R^2_b, R^3_b, R^4_b, R^4_c, R^4_d, R^5_a, R^5_b, R^5_c, and R^5_d, are defined as in claim 9.

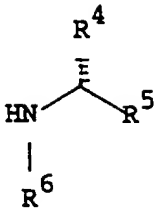
Some of the starting compounds used in the above Processes are novel and can be prepared according to the following Methods and/or by the procedures described in the following Preparations or by a conventional manner.

Method 1



(VII)

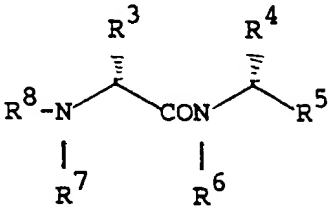
or its reactive derivative at the carboxy group, or a salt thereof



(VI)

or its reactive derivative at the amino group, or a salt thereof

[Step 1]

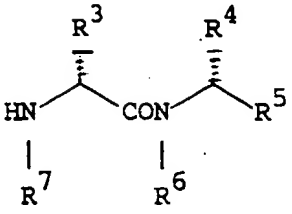


(III-a)

or a salt thereof

Removal of the amino-protective group

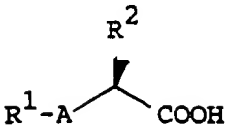
[Step 2]



(III)

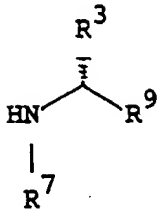
or a salt thereof

Method 2



(II)

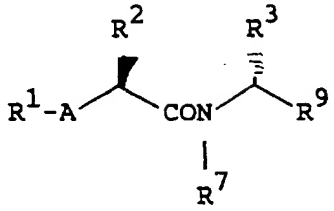
or its reactive derivative at the carboxy group, or a salt thereof



(VIII)

or its reactive derivative at the amino group, or a salt thereof

[Step 1]

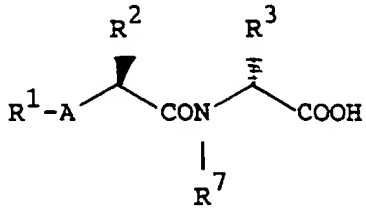


(IX)

or a salt thereof

Removal of the carboxy-protective group

[Step 2]



(V)

or a salt thereof

in which R^1, R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above,

R^8 is amino-protective group, and

R^9 is protected carboxy.

Throughout the present specification, the amino acids, peptides, protective groups, condensing agents, etc. are indicated by the abbreviations according to the IUPAC-IUB (Commission on Biological Nomenclature) which are in

common use in a field of this art.

Moreover, unless otherwise indicated, the amino acids and their residues when shown by such abbreviations are meant to be 1-configured compounds and residues, while the D-configured compounds and residues are shown with the prescript of D-.

Suitable pharmaceutically acceptable salts of the object compound (I) may be a conventional non-toxic salt and include an acid addition salt such as an organic acid salt (e.g. acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydriodide, sulfate, nitrate, phosphate, etc.), or a salt with a base such as an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), an alkali metal salt (e.g. sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), or the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention includes within the scope thereof are explained in detail as follows.

The term "C_1-C_6" is intended to mean 1 to 6, preferably 1 to 4 carbon atoms, and the term "C_7-C_{12}" is intended to mean more than 6, preferably 7 to 12 carbon atoms, unless otherwise indicated.

Suitable "acyl" may include an aliphatic acyl, an aromatic acyl, a heterocyclic acyl and an aliphatic acyl substituted with aromatic or heterocyclic group(s) derived from acids such as carboxylic, carbonic, carbamic, sulfonic acids.

The aliphatic acyl may include saturated or unsaturated, acyclic or cyclic ones, such as carbamoyl, C_1-C_6 alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, 3,3-dimethylbutyryl, 4,4-dimethylvaleryl, valeryl, isovaleryl, pivaloyl, hexanoyl, 3-methylvaleryl, etc.), C_1-C_6 alkanesulfonyl (e.g. mesyl, ethanesulfonyl, propanesulfonyl, etc.), C_1-C_6 alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, etc.), C_2-C_6 alkenoyl (e.g. acryloyl, methacryloyl, crotonoyl, etc.), (C_3-C_7)cycloalkanecarbonyl (e.g. cyclohexanecarbonyl, etc.), (C_3-C_7)cycloalkyl(C_1-C_6)alkanoyl (e.g. cyclohexylacetyl, etc.), amidino, protected carboxycarbonyl such as C_1-C_6 alkoxalyl (e.g. methoxalyl, ethoxalyl, t-butoxalyl, etc.), C_3-C_7 cycloalkyloxycarbonyl (e.g. cyclohexyloxycarbonyl, etc.), (heterocyclic acyl)(C_1-C_6)alkanoyl, wherein said heterocyclic acyl being the same as those mentioned below, such as morpholinocarbonyl(C_1-C_6)alkanoyl (e.g. 3-morpholinocarbonylpropanoyl, etc.), C_1-C_6 or C_7-C_{12} alkylcarbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, 2-methylbutylcarbamoyl, pentylcarbamoyl, 1,3-dimethylbutylcarbamoyl hexylcarbamoyl, hepthylcarbamoyl, octylcarbamoyl, nonylcarbamoyl, etc.), di(C_1-C_6)alkylcarbamoyl (e.g. N-methyl-N-ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, diisopropylcarbamoyl, dibutylcarbamoyl, diisobutylcarbamoyl, dihexylcarbamoyl, etc.), C_3-C_7 cycloalkylcarbamoyl (e.g. cyclopropylcarbamoyl, cyclobutylcarbamoyl, cyclopentylcarbamoyl, cyclohexylcarbamoyl, cycloheptylcarbamoyl, etc.), N-C_1-C_6 alkyl-N-(C_3-C_7)cycloalkylcarbamoyl (e.g. N-methyl-N-cyclopropylcarbamoyl, N-methyl-N-cyclohexylcarbonyl, N-ethyl-N-cyclohexylcarbamoyl, N-propyl-N-hexylcarbamoyl, etc.), di(C_3-C_7)cyclohexylcarbamoyl (e.g. dicyclopropylcarbamoyl, dicyclopentylcarbamoyl, dicyclohexylcarbamoyl, etc.), N-[di(C_1-C_6)alkylcarbamoyl(C_3-C_7)cycloalkyl]carbamoyl [e.g. N-(1-(or 4-)dimethylcarbamoylcyclohexyl)carbamoyl, etc.], N-[di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl(C_3-C_7)-cycloalkyl]carbamoyl [e.g. N-[1-(or 4-)(dimethylcarbamoylmethyl)cyclohexyl]carbamoyl, etc.], N-[carbamoyl(C_1-C_6)alkyl]carbamoyl [e.g. N-[1-carbamoyl-2-methylbutyl]carbamoyl, etc.], N-[N-(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl]carbamoyl [e.g. N-(1-isopropylcarbamoyl-2-methylbutyl)carbamoyl, etc.], N-[N,N-C_1-C_6 alkylenecarbamoyl(C_1-C_6)alkyl]carbamoyl [e.g. N-[2-methyl-1-(piperidinocarbonyl)butyl]carbamoyl, etc.], N-[N,N-di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl]carbamoyl [e.g. N-(dimethylcarbamoylmethyl)carbamoyl, N-[1-(or 2-)(dimethylcarbamoyl)ethyl]carbamoyl, N-[1-(dimethylcarbamoyl)-2-methylpropyl]carbamoyl, N-[2,2-dimethyl-1-(dimethylcarbamoyl)propyl]carbamoyl, N-[2-methyl-1-(dimethylcarbamoyl)butyl]carbamoyl, N-[2-methyl-1-(diethylcarbamoyl)butyl]carbamoyl, N-[3-methyl-1-(dimethylcarbamoyl)butyl]carbamoyl, N-(1-dimethylcarbamoylpentyl)carbamoyl, etc.], N-(C_1-C_6)alkyl-N-[N,N-di(C_1-C_6)alkylcarbamoyl](C_1-C_6)-alkylcarbamoyl [e.g. N-methyl-N-[1-dimethylcarbamoyl-2-methylbutyl]carbamoyl, N-methyl-N-[1-dimethylcarbamoyl-3-methylbutyl]carbamoyl, etc.], N-[N-(C_3-C_6)cycloalkylcarbamoyl(C_1-C_6)alkyl]carbamoyl [e.g. N-(1-cyclohexylcarbamoyl-2-methylbutyl)carbamoyl, etc.], and the like.

The aromatic acyl may include (C_6-C_{10})aroyl (e.g. benzoyl, toluoyl, xyloyl, naphtoyl, etc.), (C_6-C_{10})arenesulfonyl (e.g. benzenesulfonyl, tosyl, etc.), (C_6-C_{10})arylcarbamoyl (e.g. phenylcarbamoyl, tolylcarbamoyl, etc.), (C_6-C_{10})aryloxalyl (e.g. phenyloxalyl, etc.), and the like.

The heterocyclic acyl, wherein said heterocyclic group may be the same as mentioned below, may include heterocyclecarbonyl (e.g. furoyl, thienoyl, 2-(or 3- or 4-)pyridylcarbonyl, thiazolylcarbonyl, thiadiazolylcarbonyl, tetrazolylcarbonyl, piperazinylcarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, in dolylcarbonyl, etc.), C_1-C_6 or C_7-C_{12} alkyleneaminocarbonyl (e.g. aziridin-1-ylcarbonyl, azetidn-1-ylcarbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, hexahydro-1H-azepin-1-ylcarbonyl, octahydroazocin-1-ylcarbonyl, tetrahydroquinolinecarbonyl, tetrahydroisoquinolinecarbonyl, dihydropyridinecarbonyl, tetrahydropyridinecarbonyl, etc.), heterocyclic-carbamoyl wherein said heterocyclic group may be the same as mentioned below (e.g. pyridylcarbamoyl, piperidylcarbamoyl, hexahydro-1H-azepinylcarbamoyl, etc.), and the like.

The aliphatic acyl substituted with aromatic group(s) may include (C_6-C_{10})ar(C_1-C_6)alkanoyl such as phenyl(C_1-

C_6)alkanoyl (e.g. phenylacetyl, phenylpropionyl, phenylhexanoyl, naphthylacetyl etc.), (C_6-C_{10})ar(C_1-C_6)alkoxycarbonyl such as phenyl(C_1-C_6)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.), phenoxy(C_1-C_6)alkanoyl (e.g. phenoxyacetyl, phenoxypropionyl, etc.), (C_6-C_{10})ar(C_1-C_6)alkoxalyl such as phenyl(C_1-C_6)alkoxalyl(e.g. benzyloxalyl etc.), (C_6-C_{10})ar(C_2-C_6)alkenoyl such as phenyl(C_2-C_6)alkenoyl (e.g. cinnamoyl, etc.), (C_6-C_{10})ar(C_1-C_6) alkylsulfonyl (e.g. benzylsulfonyl, etc.), and the like.

The aliphatic acyl substituted with heterocyclic group(s) may include heterocyclic(C_1-C_6)alkanoyl, wherein said heterocyclic group may be the same as mentioned below (e.g. thienylacetyl, imidazolylacetyl, furylacetyl, tetrazolylacetyl, thiazolylacetyl, thiadiazolylacetyl, thienylpropionyl, thiadiazolylpropionyl, pyridylacetyl, etc.), heterocyclic-lower alkylcarbamoyl, wherein said heterocyclic group may be the same as mentioned below (e.g. pyridylmethylcarbamoyl, morpholinoethylcarbamoyl, etc.), and the like.

These acyl groups may be further substituted with one or more, preferably one to three suitable substituent(s) such as hydroxy, C_1-C_6 alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, etc.), halogen (e.g. chlorine, bromine, iodine, fluorine), carbamoyl, oxo, di(C_1-C_6)alkylcarbamoyl, amino, protected amino such as C_1-C_6 alkanoylamino (e.g. formamido, acetamido, propionamido, etc.), C_1-C_6 alkoxycarbonylamino (e.g. t-butoxycarbonylamino, etc.), C_1-C_6 alkylsulfonyl (e.g. methylsulfonyl, etc.), arylsulfonyl (e.g. phenylsulfonyl, tosyl, etc.), ar(C_1-C_6) alkyl (e.g. benzyl, etc.), C_1-C_6 alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, etc.), carboxy, protected carboxy as mentioned below, carboxy(C_1-C_6)alkyl (e.g. carboxymethyl, carboxyethyl, etc.), protected carboxy (C_1-C_6)alkyl (e.g. t-butoxycarbonylmethyl, etc.) and the like.

Suitable examples of the above acyl groups which is further substituted with one or more, preferably one to three suitable substituent(s) may be halophenyl(C_1-C_6)alkanoyl (e.g., 2-chlorophenylacetyl, etc.), (aminophenyl)(C_1-C_6) alkanoyl (e.g. 4-aminophenylacetyl, etc.), [(C_1-C_6 alkoxycarbonylamino)phenyl](C_1-C_6)alkanoyl [e.g. 4-(t-butoxycarbonylamino)phenylacetyl, etc.], amino(C_1-C_6)alkanoyl (e.g. 2-amino-3-methylpentanoyl, etc.), (C_1-C_6 alkoxycarbonylamino)(C_1-C_6)alkanoyl [e.g. 2-(t-butoxycarbonylamino)-3-methylpentanoyl, etc.), C_1-C_6 alkanoyl substituted by suitable substituent(s) such as phenyl, amino, C_1-C_6 alkoxycarbonyl amino, etc. [e.g. 2-amino-2-phenylacetyl, 2-(t-butoxycarbonylamino)-2-phenylacetyl, etc.], di(C_1-C_6)alkylpiperidinylcarbonyl [e.g. 2,6-(or 3,5-)dimethylpyperidin-1-ylcarbonyl, etc.], [di(C_1-C_6)alkylcarbamoyl]piperidinylcarbonyl [e.g. 4-(dimethylcarbamoyl)piperidin-1-ylcarbonyl, etc.], [di(C_1-C_6) alkylcarbamoyl]pyrrolidinylcarbonyl [e.g. 2-(dimethylcarbamoyl)pyrrolidin-1-ylcarbonyl, etc.], piperazinylcarbonyl substituted by suitable substituent(s) such as C_1-C_6 alkyl, oxo, etc. [e.g. 4-methyl-3-oxo-2-(1-methylpropyl)piperazin-1-ylcarbonyl, etc.], N-(C_1-C_6)alkyl-N-[hydroxy(C_1-C_6)alkyl]carbamoyl [e.g. N-methyl-N-(2-hydroxyethyl)carbamoyl, etc.], N-[hydroxy(C_1-C_6)alkyl]carbamoyl [e.g. N-{1-(hydroxymethyl)-3-methylbutyl}carbamoyl, etc.], N-[(C_3-C_7)cycloalkyl (C_1-C_6)alkyl]carbamoyl [e.g. N-(cyclohexylmethyl)carbamoyl, etc.], N-[carboxy(C_1-C_6)alkyl]carbamoyl [e.g. N-(1-carboxy-2-methylbutyl)carbamoyl, etc.], N[(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl]carbamoyl [e.g. N-(1-methoxycarbonyl-2-methylbutyl)carbamoyl, etc.], (oxoheterocyclic)carbamoyl wherein said heterocyclic group may be the same as mentioned below such as {oxo(hexahydro-1H-azepinyl)}carbamoyl (e.g. ε-caprolactam-3-yl, etc.), etc., N-[N-(C_1-C_6)alkoxycarbonylpiperidinyl]carbamoyl [e.g. N-(N-ethoxycarbonylpiperidin-4-yl)carbamoyl, etc.], N-[N,N-di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl]carbamoyl substituted by phenyl or cyclo(C_1-C_6)alkyl [e.g. N-{1-(N,N-dimethylcarbamoyl)-1-phenylmethyl}carbamoyl, N-{1-(N,N-dimethylcarbamoyl)-1-cyclohexylmethyl}-carbamoyl, etc.], N-[hydroxy(C_3-C_7)cycloalkyl]carbamoyl [e.g. N-(4-hydroxycyclohexyl)carbamoyl, etc.], N-(C_1-C_6)alkoxyphenylcarbamoyl [e.g. N-(4-methoxyphenyl)carbamoyl, etc.], N-(C_1-C_6 alkanoylamino)carbamoyl [e.g. N-(2-methylpropanoylamino)carbamoyl, etc.], and the like.

Preferable example of acyl may be carbamoyl, C_1-C_6 alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, 3,3-dimethylbutyryl, 4,4-dimethylvaleryl, valeryl, isovaleryl, pivaloyl, hexanoyl, 3-methylvaleryl, etc.), C_1-C_6 alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, etc.), C_2-C_6 alkenoyl (e.g. acryloyl, methacryloyl, crotonoyl, etc.), (C_3-C_7)cycloalkanecarbonyl (e.g. cyclohexanecarbonyl, etc.), (C_3-C_7)cycloalkyl(C_1-C_6)alkanoyl (e.g. cyclohexylacetyl, etc.), C_3-C_7 cycloalkyloxycarbonyl (e.g. cyclohexyloxycarbonyl, etc.), morpholinocarbonyl(C_1-C_6)alkanoyl (e.g. 3-morpholinocarbonylpropanoyl, etc.), C_1-C_6 or C_7-C_{12} alkylcarbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, 2-methylbutylcarbamoyl, pentylcarbamoyl, 1,3-dimethylbutylcarbamoyl hexylcarbamoyl, hepthylcarbamoyl, octylcarbamoyl, nonylcarbamoyl, etc.), di(C_1-C_6)alkylcarbamoyl (e.g. N-methyl-N-ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, diisopropylcarbamoyl, dibutylcarbamoyl, diisobutylcarbamoyl, dihexylcarbamoyl, etc.), C_3-C_7 cycloalkylcarbamoyl (e.g. cyclopropylcarbamoyl, cyclobutylcarbamoyl, cyclopentylcarbamoyl, cyclohexylcarbamoyl, cycloheptylcarbamoyl, etc.), N-C_1-C_6 alkyl-N-(C_3-C_7)cycloalkylcarbamoyl (e.g. N-methyl-N-cyclopropylcarbamoyl, N-methyl-N-cyclohexylcarbamoyl, N-ethyl-N-cyclohexylcarbamoyl, N-propyl-N-hexylcarbamoyl, etc.), di(C_3-C_7)cyclohexylcarbamoyl (e.g. dicyclopropylcarbamoyl, dicyclopentylcarbamoyl, dicyclohexylcarbamoyl, etc.), N-[di(C_1-C_6) alkylcarbamoyl(C_3-C_7)cycloalkyl]carbamoyl [e.g. N-(1-(or 4-)dimethylcarbamoylcyclohexyl)carbamoyl, etc.], N-[di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl(C_3-C_7)-cycloalkyl]carbamoyl [e.g. N-[1-(or 4-)(dimethylcarbamoylmethyl)cyclohexyl] carbamoyl, etc.], N-[carbamoyl(C_1-C_6)alkyl]carbamoyl [e.g. N-[1-carbamoyl-2-methylbutyl]carbamoyl, etc.], N-[N-(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl]carbamoyl [e.g. N-(1-isopropylcarbamoyl-2-methylbutyl)carbamoyl, etc.], N-[N,N-C_1-

C_6 alkylenecarbamoyl(C_1-C_6)alkyl]carbamoyl [e.g. N-[2-methyl-1-(piperidinocarbonyl)butyl]carbamoyl, etc.], N-[N,N-di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl]carbamoyl [e.g. N-(dimethylcarbamoylmethyl)carbamoyl, N-[1-(or 2-)(dimethylcarbamoyl)ethyl]carbamoyl, N-[1-(dimethylcarbamoyl)-2-methylpropyl]carbamoyl, N-[2,2-dimethyl-1-(dimethylcarbamoyl)propyl]carbamoyl, N-[2-methyl-1-(dimethylcarbamoyl)butyl]carbamoyl, N-[2-methyl-1-(diethylcarbamoyl)butyl]carbamoyl, N-[3-methyl-1-(dimethylcarbamoyl)butyl]carbamoyl, N-(1-dimethylcarbamoylpentyl)carbamoyl, etc.], N-(C_1-C_6)alkyl-N-[N,N-di(C_1-C_6)alkylcarbamoyl](C_1-C_6)-alkylcarbamoyl [e.g. N-methyl-N-[1-dimethylcarbamoyl-2-methylbutyl]carbamoyl, N-methyl-N-[1-dimethylcarbamoyl-3-methylbutyl]carbamoyl, etc.], N-[N-(C_3-C_6)cycloalkylcarbamoyl(C_1-C_6)alkyl]carbamoyl [e.g. N-(1-cyclohexylcarbamoyl-2-methylbutyl)carbamoyl, etc.], (C_6-C_{10})aroyl (e.g. benzoyl, toluoyl, xyloyl, naphtoyl, etc.), (C_6-C_{10})arylcarbamoyl (e.g. phenylcarbamoyl, tolylcarbamoyl, etc.), (C_6-C_{10}) aryloxalyl (e.g. phenyloxalyl, etc.), furoyl, thienoyl, 2-(or 3- or 4-)pyridylcarbonyl, thiazolylcarbonyl, thiadiazolylcarbonyl, tetrazolylcarbonyl piperazinylcarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, indolylcarbonyl, C_1-C_6 alkyleneaminocarbonyl (e.g. aziridin-1-ylcarbonyl, azetidin-1-ylcarbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, hexahydro-1H-azepin-1-ylcarbonyl, octahydroazocin-1-ylcarbonyl, tetrahydroquinolinecarbonyl, tetrahydroisoquinolinecarbonyl, dihydropyridinecarbonyl, tetrahydropyridinecarbonyl, etc.), pyridylcarbamoyl, piperidylcarbamoyl, hexahydro-1H-azepinylcarbamoyl, (C_6-C_{10})ar(C_1-C_6)alkanoyl such as phenyl(C_1-C_6)alkanoyl (e.g. phenylacetyl, phenylpropionyl, phenylhexanoyl, naphthylacetyl, etc.), (C_6-C_{10})ar(C_1-C_6)alkoxycarbonyl such as phenyl(C_1-C_6)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.), (C_6-C_{10})ar(C_1-C_6)alkoxalyl such as phenyl)(C_1-C_6)alkoxalyl (e. g. benzyloxalyl etc.), (C_6-C_{10})ar(C_2-C_6)alkenoyl such as phenyl(C_2-C_6)alkenoyl (e.g. cinnamoyl, etc.), (C_6-C_{10})ar(C_1-C_6)alkylsulfonyl (e.g. benzylsulfonyl, etc.), thienylacetyl, imidazolylacetyl, furylacetyl, tetrazolylacetyl, thiazolylacetyl, thiadiazolylacetyl, thienylpropionyl, thiadiazolylpropionyl, pyridylacetyl, pyridylmethylcarbamoyl, morpholinoethylcarbamoyl, halophenyl(C_1-C_6)alkanoyl (e.g. 2-chlorophenylacetyl, etc.), (aminophenyl)(C_1-C_6)alkanoyl (e.g. 4-aminophenylacetyl, etc.), [(C_1-C_6 alkoxycarbonylamino)phenyl](C_1-C_6)alkanoyl [e.g. 4-(t-butoxycarbonylamino)phenylacetyl, etc.], amino(C_1-C_6)alkanoyl (e.g. 2-amino-3-methylpentanoyl, etc.), (C_1-C_6 alkoxycarbonylamino)(C_1-C_6)alkanoyl [e. g. 2-(t-butoxycarbonylamino)-3-methylpentanoyl, etc.], C_1-C_6 alkanoyl substituted by suitable substituent(s) such as phenyl, amino, C_1-C_6 alkoxycarbonylamino [e.g. 2-amino-2-phenylacetyl, 2-(t-butoxycarbonylamino)-2-phenylacetyl, etc.], etc., di(C_1-C_6)alkylpiperidinylcarbonyl [e.g. 2,6-(or 3,5-)dimethylpiperidin-1-ylcarbonyl, etc.], [di(C_1-C_6)alkylcarbamoyl]piperidinylcarbonyl [e.g. 4-(dimethylcarbamoyl)piperidin-1-ylcarbonyl, etc.], [di(C_1-C_6)alkylcarbamoyl]pyrrolidinylcarbonyl [e.g. 2-(dimethylcarbamoyl)pyrrolidin-1-ylcarbonyl, etc.], piperazinylcarbonyl substituted by suitable substituent(s) such as C_1-C_6 alkyl, oxo, etc. [e.g. 4-methyl-3-oxo-2-(1-methylpropyl)piperazin-1-ylcarbonyl, etc.], N-(C_1-C_6)alkyl-N-[hydroxy(C_1-C_6)alkyl]carbamoyl [e.g. N-methyl-N-(2-hydroxyethyl)carbamoyl, etc.], N-[hydroxy(C_1-C_6) alkyl]carbamoyl [e.g. N-{1-(hydroxymethyl)-3-methylbutyl}carbamoyl, etc.], N-[(C_3-C_7)cycloalkyl(C_1-C_6)alkyl]carbamoyl [e.g. N-(cyclohexylmethyl)carbamoyl, etc.], N-[carboxy(C_1-C_6)alkyl]carbamoyl [e.g. N-(1-carboxy-2-methylbutyl)carbamoyl, etc.], N-[(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl]carbamoyl [e.g. N-(1-methoxycarbonyl-2-methylbutyl) carbamoyl, etc.], (oxoheterocyclic)carbamoyl such as {oxo(hexahydro-1H-azepinyl)}carbamoyl (e.g. ε-caprolactam-3-yl, etc.), etc., N-[N-(C_1-C_6)alkoxycarbonylpiperidinyl]carbamoyl [e.g. N-(N-ethoxycarbonylpiperidin-4-yl)carbamoyl, etc.], N-[N,N-di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl]carbamoyl substituted by phenyl or cyclo(C_1-C_6)alkyl [e.g. N-{1-(N, N-dimethylcarbamoyl)-1-phenylmethyl}carbamoyl, N-{1-(N,N-dimethylcarbamoyl)-1-cyclohexylmethyl}carbamoyl, etc.], N-[hydroxy(C_3-C_7)cycloalkyl]carbamoyl [e.g. N-(4-hydroxycyclohexyl)carbamoyl, etc.], N-(C_1-C_6)alkoxyphenyl) carbamoyl [e.g. N-(4-methoxyphenyl)carbamoyl, etc.], N-(C_1-C_6 alkanoylamino)carbamoyl [e.g. N-(2-methylpropanoylamino)carbamoyl, etc.], and the like.

Suitable "C_1-C_6 alkyl" may include a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like, in which the most preferred example may be isobutyl, 1-methylpropyl, n-butyl and 2,2-dimethylpropyl for R^2, and methyl for R^7.

Suitable "C_1-C_6 alkylene" may include a straight or branched one such as methylene, ethylene, propylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, and the like, in which the most preferred example may be methylene.

Suitable "protected carboxy" may include esterified carboxy and amidated carboxy as mentioned above.

"Esterified carboxy" can be referred to the ones as mentioned below.

Suitable examples of the ester moiety of an esterified carboxy may be C_1-C_6 alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, hexyl ester, etc.); C_1-C_6 alkanoyloxy(C_1-C_6)alkyl ester [e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1-(or 2-)acetoxyethyl ester, 1-(or 2- or 3-)acetoxypropyl ester, 1-(or 2- or 3- or 4-)acetoxybutyl ester, 1-(or 2-)propionyloxyethyl ester, 1-(or 2- or 3-)propionyloxypropyl ester, 1-(or 2-)butyryloxyethyl ester, 1-(or 2-)isobutyryloxyethyl ester, 1-(or 2-)pivaloyloxyethyl ester, 1-(or 2-)hexanoyloxyethyl ester, isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester, 3,3-dimethylbutyryloxymethyl ester, 1-(or 2-)pentanoyloxyethyl ester, etc.]; C_6-C_{10} aroyl(C_1-C_6)alkyl ester (e.g. phenacyl ester, etc.); C_1-C_6 alkanesulfonyl(C_1-C_6)alkyl ester (e.g. 2-mesylethyl ester, etc.); mono(or di or tri)halo(C_1-C_6)alkyl ester (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.); C_1-C_6 alkoxycarbonyloxy(C_1-C_6)alkyl ester [e.g. methoxycarbonyloxymethyl ester, ethoxycarbonyloxyme-

thyl ester, propoxycarbonyloxymethyl ester, t-butoxycarbonyloxymethyl ester, 1-(or 2-)methoxycarbonyloxyethyl ester, 1-(or 2-)ethoxycarbonyloxyethyl ester, 1-(or 2-)isopropoxycarbonyloxyethyl ester, etc.]; phthalidylidene(C_1-C_6)alkyl ester; or (5-C_1-C_6 alkyl-2-oxo-1,3-dioxol-4-yl)(C_1-C_6)alkyl ester [e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, etc.]; C_2-C_6 alkenyl ester (e.g. vinyl ester, allyl ester, etc.); C_2-C_6 alkynyl ester (e.g. ethynyl ester, propynyl ester, etc.); C_6-C_{10}ar(C_1-C_6)alkyl ester which may have at least one suitable substituent(s) (e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-t-butylbenzyl ester, etc.); C_6-C_{10} aryl ester which may have at least one suitable substituent(s) (e.g. phenyl ester, 4-chlorophenyl ester, tolyl ester, t-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, etc.); phthalidyl ester; and the like; preferably C_1-C_6 alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, hexyl ester, etc.) C_6-C_{10}ar(C_1-C_6)alkyl ester (e.g. benzyl ester, phenethyl ester, trityl ester, benzhydryl ester, etc.), and C_6-C_{10} aroyl(C_1-C_6) alkyl ester.

Preferable examples of the esterified carboxy thus defined may be C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl and benzoyl(C_1-C_6)alkoxycarbonyl, and the most preferable one may be methoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl and phenacyloxycarbonyl.

Suitable "carboxy(C_1-C_6)alkyl" means aforementioned C_1-C_6 alkyl which is substituted by carboxy, wherein the preferable examples may be carboxymethyl, carboxyethyl, carboxypropyl and carboxybutyl for R^5.

Suitable "protected carboxy(C_1-C_6)alkyl" means aforementioned C_1-C_6 alkyl which is substituted by above-mentioned "protected carboxy", wherein more preferable example may be C_1-C_6 alkoxycarbonyl(C_1-C_6)alkyl, phenyl(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl and benzoyl(C_1-C_6)alkoxycarbonyl, and the most preferable one may be methoxycarbonylmethyl, methoxycarbonylethyl, methoxycarbonylpropyl, methoxycarbonylbutyl, phenacyloxycarbonylmethyl, phenacyloxycarbonylethyl, phenacyloxycarbonylpropyl and phenacyloxycarbonylbutyl for R^5.

Said "amidated carboxy" can be referred to the ones as defined in Claim 4.

Suitable examples of the amidated carboxy may include -carbamoyl,

-mono(or di)(C_1-C_6)alkylcarbamoyl wherein the C_1-C_6 alkyl group may be the same as those mentioned above (e.g. methylcarbamoyl, ethylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, 3-methylbutylcarbamoyl, isobutylcarbamoyl, pentylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, etc.),

and further said C_1-C_6 alkyl is optionally substituted by one or two substituents selected from

carboxy;

protected carboxy as mentioned above such as C_1-C_6 alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, etc.), C_6-C_{10}ar(C_1-C_6)alkoxycarbonyl, preferably phenyl(C_1-C_6)alkoxycarbonyl (e.g. benzyloxycarbonyl, etc.), C_6-C_{10} aroyl(C_1-C_6)alkoxycarbonyl, preferably benzoyl(C_1-C_6)alkoxycarbonyl (e.g. phenacyloxycarbonyl, etc.);

C_6-C_{10} aryl (e.g. phenyl, naphthyl, etc.); saturated or unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) (e.g. pyridyl, pyrrolidinyl, etc.),

wherein said heterocyclic group may be further substituted by suitable substituent(s) selected from oxo, carboxy, protected carboxy as mentioned above and carbamoyl, for example, oxopyrrolidinyl substituted by carboxy, C_1-C_6 alkoxycarbonyl or carbamoyl [e.g.

2-oxo-5-carboxypyrrolidinyl,
2-oxo-5-ethoxycarbonylpyrrolidinyl,
2-oxo-5-carbamoylpyrrolidinyl, etc.);

C_3-C_7 cycloalkyl optionally substituted by carboxy or protected carboxy as mentioned above such as C_1-C_6 alkoxycarbonyl (e.g. carboxycyclohexyl, ethoxycarbonylcyclohexyl, etc.);

-(C_3-C_7)cycloalkylcarbamoyl (e.g. cyclohexylcarbamoyl,),

-carbamoyl substituted by amino or di(C_1-C_6)alkylamino [e.g. N-aminocarbamoyl, N-(dimethylamino)carbamoyl,],

-N-(optionally substituted heterocyclic)carbamoyl wherein the heterocyclic moiety is

saturated 5 or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 5 or 6-membered heteromonocyclic group

containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

each of said heterocyclic group may be substituted by substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro and cyano, for example, thiazolylcarbamoyl, benzothiazolylcarbamoyl, morpholinocarbamoyl, N-(C_1-C_6 alkylthiadiazolyl)carbamoyl (e.g. methylthiadiazolylcarbamoyl, etc.),

-C_3-C_6 alkyleneaminocarbonyl (e.g. pyrrolidin-1-ylcarbonyl, hexahydro-1H-azepin-1-ylcarbonyl, etc.),

said alkylene moiety being optionally substituted by carboxy or protected carboxy as mentioned above such as C_1-C_6 alkoxycarbonyl [e.g. carboxypyrrolidin-1-ylcarbonyl, (methoxycarbonyl)pyrrolidin-1-ylcarbonyl, (ethoxycarbonyl)pyrrolidin-1-ylcarbonyl, etc.],
or said C_3-C_6 alkylene moiety being optionally interrupted by other hetero atom(s) such as nitrogen, oxygen or sulfur (e.g. morpholinocarbonyl, etc.),

-C_1-C_6 alkylsufonylcarbamoyl (e.g. methylsufonylcarbamoyl, etc.),
C_6-C_{10} arylsulfonylcarbamoyl (e.g. benzenesulfonylcarbamoyl, etc.), preferably
-carbamoyl,
-(C_1-C_6)alkylcarbamoyl wherein the C_1-C_6 alkyl group may be the same as those mentioned above (e.g. methylcarbamoyl, ethylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, 3-methylbutylcarbamoyl, isobutylcarbamoyl, pentylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, etc.),
and further said C_1-C_6 alkyl is substituted by one or two substituents selected from

carboxy;
protected carboxy as mentioned above such as C_1-C_6 alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, etc.), C_6-C_{10} ar(C_1-C_6)alkoxycarbonyl, preferably phenyl(C_1-C_6)alkoxycarbonyl (e.g. benzyloxycarbonyl, etc.), C_6-C_{10}aroyl(C_1-C_6)alkoxycarbonyl, preferably benzoyl(C_1-C_6)alkoxycarbonyl (e.g. phenacyloxycarbonyl, etc.);

-(C_3-C_7)cycloalkylcarbamoyl (e.g. cyclohexylcarbamoyl, etc.),
-N-(heterocyclic)carbamoyl such as

5- or 6-membered saturated heteromonocycliccarbamoyl, in which the heterocyclic ring contains one nitrogen atom and one oxygen atom,
5- or 6-membered aromatic heteromonocycliccarbamoyl, in which the heterocyclic ring contains one to three nitrogen atoms,
5- or 6-membered aromatic heteromonocycliccarbamoyl, in which the heterocyclic ring contains one to two nitrogen atoms and one sulfur atom and may be substituted by C_1-C_6 alkyl,
9- or 10-membered benzene-condensed heterocyclic carbamoyl, in which the heterocyclic ring contains one to two nitrogen atoms and one sulfur atom,
5- or 6-membered saturated heteromonocyclic(C_1-C_6)alkylcarbamoyl, in which the heterocyclic ring contains one nitrogen atom and one oxygen atom,
5- or 6-membered aromatic heteromonocyclic(C_1-C_6)-alkylcarbonyl, in which the heterocyclic ring contains one to three nitrogen atoms,
carbazoyl or di(C_1-C_6) alkylcarbazoyl,

-C_3-C_6 alkyleneaminocarbonyl , (e.g. pyrrolidin-1-ylcarbonyl, hexahydro-1H-azepin-1-ylcarbonyl, etc.),
optionally substituted by carboxy or protected carboxy as mentioned above such as C_1-C_6 alkoxycarbonyl [e.g. carboxypyrrolidin-1-ylcarbonyl, (methoxycarbonyl)pyrrolidin-1-ylcarbonyl, (ethoxycarbonyl)pyrrolidin-1-ylcarbonyl, etc.],
-C_1-C_6 alkylsufonylcarbamoyl (e.g. methylsulfonylcarbamoyl, etc.),
C_6-C_{10} arylsulfonylcarbamoyl (e.g. benzenesulfonylcarbamoyl, etc.),
-N- or N,N-di(C_1-C_6)alkylcarbamoyl,
-N-(C_1-C_6)alkyl-N-[carboxy- or protected carboxy(C_1-C_6)alkyl]carbamoyl,
-C_6-C_{10} ar(C_1-C_6)alkylcarbamoyl,
-carboxy- or protected carboxy-substituted C_6-C_{10} ar (C_1-C_6)alkylcarbamoyl,
-N-[carboxy- or protected carboxy-substituted (C_3-C_7)cycloalkyl(C_1-C_6)alkyl]carbamoyl
-carboxy- or protected carboxy-substituted 5- or 6-membered aromatic heterocyclic-(C_1-C_6)alkylcarbamoyl, in which the heterocyclic ring contains one to three nitrogen atoms,
-[C_3-C_{10} alkylene amino[(C_1-C_6)alkyl]carbamoyl substituted by one or two substituents selected from oxo, carboxy,

protected carboxy and carbamoyl,
-morpholinocarbonyl interrupted by other hetero atom(s) such as nitrogen, oxygen or sulfur (e.g. morpholinocarbonyl, etc.),
-C_1-C_6 alkylsulfonylcarbamoyl (e.g. methylsulfonylcarbamoyl, etc.),
-C_6-C_{10} arylsulfonylcarbamoyl (e.g. benzenesulfonylcarbamoyl, etc.).

Preferable example of the amidated carboxy thus defined may be:

-carbamoyl,
-N- or N,N-di(C_1-C_6) alkyl carbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, 3-methylbutylcarbamoyl, isobutylcarbamoyl, pentylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, etc.),
-N-(C_1-C_6)alkyl-N-[carboxy(C_1-C_6)alkyl]carbamoyl [e.g. N-methyl-N-(carboxymethyl)carbamoyl, etc.]
-N-(C_1-C_6)alkyl-N-[protected carboxy(C_1-C_6)alkyl]carbamoyl such as N-(C_1-C_6)alkyl-N-[C_1-C_6 alkoxycarbonyl(C_1-C_6-alkyl]carbamoyl [e.g. N-methyl-N-(methoxycarbonylmethyl)carbamoyl, etc.],
-N-[carboxy(C_1-C_6)alkyl]carbamoyl [e.g. N-(carboxymethyl)-carbamoyl, N-(2-carboxyethyl)carbamoyl, N-(3-carboxypropyl)carbamoyl, N-(4-carboxybutyl)carbamoyl, N-(5-carboxypentyl)-carbamoyl, N-(1-carboxyethyl)carbamoyl, N-(1-carboxy-2-methylpropyl)carbamoyl, N-(1-carboxy-3-methylbutyl)carbamoyl, N-(1,2-dicarboxyethyl) carbamoyl, etc.],
-N-[protected carboxy(C_1-C_6)alkyl]carbamoyl such as N-[C_1-C_6 alkoxycarbonyl(C_1-C_6)alkyl]carbamoyl [e.g N-(methoxycarbonylmethyl)carbamoyl, N-(2-methoxycarbonylethyl)carbamoyl, N-(3-methoxycarbonylpropyl)carbamoyl, N-(4-methoxycarbonylbutyl)carbamoyl, N-(5-methoxycarbonylpentyl)carbamoyl, N-[1,2-bis(methoxycarbonyl)ethyl]carbamoyl, etc.), N-[C_6-C_{10}ar(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl]carbamoyl, preferably N-[phenyl(C_1-C_6)alkoxycarbonyl(C_1-C_6)-alkyl]carbamoyl [e.g. N-(benzyloxycarbonylmethyl)-carbamoyl, N-(2-benzyloxycarbonylethyl)carbamoyl, N-(3-benzyloxycarbonylpropyl)carbamoyl, N-(4-benzyloxycarbonylbutyl)carbamoyl, N-(5-benzyloxycarbonylpentyl)carbamoyl, etc.), N-[{C_6-C_{10}aroyl(C_1-C_6)alkoxy}(C_1-C_6)alkyl]carbamoyl, preferably benzoyl(C_1-C_6)alkoxy(C_1-C_6)alkyl]carbamoyl [e.g. N-(phenacyloxycarbonylmethyl)carbamoyl, N-(2-phenacyloxycarbonylethyl)carbamoyl, N-(3-phenacyloxycarbonylpropyl)carbamoyl, N-(4-phenacyloxycarbonylbutyl)carbamoyl, N-(5-phenacyloxycarbonylpentyl)carbamoyl, N-(1-phenacyloxyethyl)carbamoyl, N-(1-phenacyloxy-2-methylpropyl)carbamoyl, N-(1-phenacyloxy-3-methylbutyl)carbamoyl, etc.],
-N-[carboxy(C_1-C_6)alkyl]carbamoyl substituted by C_6-C_{10} aryl such as N-[carboxy(C_1-C_6)alkyl]carbamoyl substituted by phenyl or naphthyl [e.g. N-(1-carboxy-2-phenylethyl)carbamoyl, etc.],
-N-[protected carboxy(C_1-C_6)alkyl]carbamoyl substituted by C_6-C_{10} aryl such as N-[{C_1-C_6 alkoxycarbonyl}(C_1-C_6)alkyl]carbamoyl substituted by phenyl or naphthyl [e.g. N-(1-ethoxycarbonyl-2-phenylethyl)carbamoyl, etc.],
-N-[carboxy(C_1-C_6)alkyl]carbamoyl substituted by heterocyclic group such as pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, and its N-oxide, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 2H-1,2,3-triazolyl, etc.), tetrazolyl and dihydrotriazinyl [e.g. N-{1-carboxy-2-(pyridin-2-yl)ethyl}carbamoyl, etc.],
-N-[protected carboxy(C_1-C_6)alkyl]carbamoyl substituted by heterocyclic group such as N-[C_1-C_6 alkoxycarbonyl-(C_1-C_6)alkyl]carbamoyl subsituted by pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, and its N-oxide, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl, tetrazolyl or dihydrotriazinyl [e.g. N-{1-ethoxycarbonyl-2- (pyridin-2-yl)ethyl}carbamoyl, etc.],
-N-[C_6-C_{10} aryl(C_1-C_6)alkyl]carbamoyl such as phenyl(C_1-C_6)alkylcarbamoyl (e.g. N-benzylcarbamoyl, etc.),
-N-[{carboxy(C_3-C_7)cycloalkyl}(C_1-C_6)alkyl]carbamoyl [e.g. N-(4-carboxycyclohexylmethyl)carbamoyl, etc.],
-N-[{protected carboxy(C_3-C_7)cycloalkyl}(C_1-C_6)alkyl]carbamoyl such as N-[{C_1-C_6 alkoxycarbonyl(C_3-C_7)-cycloalkyl}(C_1-C_6)alkyl]carbamoyl [e.g. N-(4-ethoxycarbonylcyclohexylmethyl)carbamoyl, etc.],
-N-[heterocyclic-(C_1-C_6)alkyl]carbamoyl, said heterocyclic group being azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, pyrazolidinyl and piperazinyl, such as N-[pyrrolidinyl(C_1-C_6)alkyl]carbamoyl [e.g. N-{2-(pyrrolidin-1-yl) ethyl}carbamoyl, etc.],
wherein said heterocyclic group may be substituted by suitable substituent(s) such as oxo, carboxy, protected carboxy as mentioned above and carbamoyl, for example, oxopyrrolidinyl substituted by carboxy, C_1-C_6 alkoxycarbonyl or carbamoyl [e.g. 2-oxo-5-carboxypyrrolidinyl, 2-oxo-5-ethoxycarbonylpyrrolidinyl, 2-oxo-5-carbamoylpyrrolidinyl, etc.);
-(C_3-C_7)cycloalkylcarbamoyl (e.g. cyclohexylcarbamoyl, etc.),
-carbamoyl substituted by amino or di(C_1-C_6)alkylamino [e.g. N-aminocarbamoyl, N-(dimethylamino)carbamoyl, etc.],
-N-(optionally substituted heterocyclic)carbamoyl wherein the heterocyclic moiety being thiazolyl, 1,2-thiazolyl, thiazolinyl, thiadiazolyl, thiazolidinyl, benzothiazolyl, benzothiadiazolyl, morpholinyl, [e.g. thiazolylcarbamoyl, benzothiazolylcarbamoyl and morpholinylcarbamoyl, etc.],.
each of said heterocyclic group may be substituted by C_1-C_6 alkyl, for example, N-(C_1-C_6 alkylthiadiazolyl)

carbamoyl (e.g. methylthiadiazolyl, etc.),
-C_3-C_6 alkyleneaminocarbonyl (e.g. pyrrolidin-1-ylcarbonyl, hexahydro-1H-azepin-1-ylcarbonyl, etc.),
-C_3-C_6 alkyleneaminocarbonyl substituted by carboxy or protected carboxy such as C_1-C_6 alkoxycarbonyl [e.g. 2-carboxypyrrolidin-1-ylcarbonyl, 2-(methoxycarbonyl)pyrrolidin-1-ylcarbonyl, 2-(ethoxycarbonyl)pyrrolidin-1-ylcarbonyl, etc.],
-C_3-C_6 alkyleneaminocarbonyl wherein said C_3-C_6 alkylene being interrupted by oxygen (e.g. morpholinocarbonyl, etc.),
-C_1-C_6 alkylsufonylcarbamoyl (e.g. methylsufonylcarbamoyl, etc.),
-C_6-C_{10} arylsulfonylcarbamoyl (e.g. benzenesulfonylcarbamoyl, etc.), and the like, preferably.
-carbamoyl
-N- or N,N-di(C_1-C_6) alkyl carbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, 3-methylbutylcarbamoyl, isobutylcarbamoyl, pentylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, etc.),
-N-(C_1-C_6)alkyl-N-[carboxy(C_1-C_6)alkyl]carbamoyl [e.g. N-methyl-N-(carboxymethyl)carbamoyl, etc.]
-N-(C_1-C_6)alkyl-N-[protected carboxy(C_1-C_6)alkyl]carbamoyl such as N-(C_1-C_6)alkyl-N-[C_1-C_6 alkoxycarbonyl(C_1-C_6)-alkyl]carbamoyl [e.g. N-methyl-N-(methoxycarbonylmethyl)carbamoyl, etc.],
-N-[carboxy(C_1-C_6)alkyl]carbamoyl [e.g. N-(carboxymethyl)carbamoyl, N-(2-carboxyethyl)carbamoyl, N-(3-carboxypropyl)carbamoyl, N-(4-carboxybutyl)carbamoyl, N-(5-carboxypentyl)carbamoyl, N-(1-carboxyethyl)carbamoyl, N-(1-carboxy-2-methylpropyl)carbamoyl, N-(1-carboxy-3-methylbutyl)carbamoyl, N-(1,2-dicarboxyethyl) carbamoyl, etc.],
-N-[protected carboxy(C_1-C_6)alkyl]carbamoyl such as N-[C_1-C_6 alkoxycarbonyl(C_1-C_6)alkyl]carbamoyl [e.g. N-(methoxycarbonylmethyl)carbamoyl, N-(2-methoxycarbonylethyl)carbamoyl, N-(3-methoxycarbonylpropyl)carbamoyl, N-(4-methoxycarbonylbutyl)carbamoyl, N-(5-methoxycarbonylpentyl)carbamoyl, N-[1,2-bis(methoxycarbonyl)ethyl]carbamoyl, etc.), N-[C_6-C_{10}ar(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl]carbamoyl, preferably N-[phenyl(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl]carbamoyl [e.g. N-(benzyloxycarbonylmethyl)carbamoyl, N-(2-benzyloxycarbonylethyl)carbamoyl, N-(3-benzyloxycarbonylpropyl)carbamoyl, N-(4-benzyloxycarbonylbutyl)carbamoyl, N-(5-benzyloxycarbonylpentyl)carbamoyl, etc.), N-[{C_6-C_{10}aroyl(C_1-C_6)alkoxy}(C_1-C_6)alkyl]carbamoyl, preferably benzoyl(C_1-C_6)alkoxy(C_1-C_6)alkyl]carbamoyl [e.g. N-(phenacyloxycarbonylmethyl)carbamoyl, N-(2-phenacyloxycarbonylethyl)carbamoyl, N-(3-phenacyloxycarbonylpropyl)carbamoyl, N-(4-phenacyloxycarbonylbutyl)carbamoyl, N-(5-phenacyloxycarbonylpentyl)carbamoyl, N-(1-phenacyloxyethyl)carbamoyl, N-(1-phenacyloxy-2-methylpropyl)carbamoyl, N-(1-phenacyloxy-3-methylbutyl)carbamoyl, etc.],
-N-[carboxy(C_1-C_6)alkyl]carbamoyl substituted by aryl such as N-[carboxy(C_1-C_6)alkyl]carbamoyl substituted by phenyl or naphthyl [e.g. N-(1-carboxy-2-phenylethyl)carbamoyl, etc.],
-N-[protected carboxy(C_1-C_6)alkyl]carbamoyl substituted by aryl such as N-[{C_1-C_6 alkoxycarbonyl}(C_1-C_6)alkyl] carbamoyl substituted by phenyl on naphthyl [e.g. N-(1-ethoxycarbonyl-2-phenylethyl)carbamoyl, etc.],
-N-[carboxy(C_1-C_6)alkyl]carbamoyl substituted by heterocyclic group such as pyrrolyl, imidazolyl, pyrazolyl, pyridyl, and its N-oxide, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 2H-1,2,3-triazolyl, etc.), [e.g. N-{1-carboxy-2-(pyridin-2-yl)ethyl}carbamoyl, etc.],
-N-[protected carboxy(C_1-C_6)alkyl]carbamoyl subsituted by heterocyclic group such as N-[C_1-C_6 alkoxycarbonyl (C_1-C_6)alkyl]carbamoyl subsituted by pyrrolyl, imidazolyl, pyrazolyl, pyridyl, and its N-oxide, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl, [e.g. N-{1-ethoxycarbonyl-2- (pyridin-2-yl)ethyl)carbamoyl, etc.],
-N-[C_6-C_{10}aryl(C_1-C_6)alkyl]carbamoyl such as phenyl(C_1-C_6)alkylcarbamoyl (e.g. N-benzylcarbamoyl, etc.),
-N-[{carboxy(C_3-C_7)cycloalkyl}(C_1-C_6)alkyl]carbamoyl [e.g. N-(4-carboxycyclohexylmethyl)carbamoyl, etc.],
-N-[{protected carboxy(C_3-C_7)cycloalkyl}(C_1-C_6)alkyl]carbamoyl such as N-[{C_1-C_6 alkoxycarbonyl(C_3-C_7)cycloalkyl}(C_1-C_6)alkyl]carbamoyl [e.g. N-(4-ethoxycarbonylcyclohexylmethyl)carbamoyl, etc.],
-N-[heterocyclic-(C_1-C_6)alkyl]carbamoyl, said heterocyclic group being pyrrolidinyl, imidazolidinyl, and such as N-[pyrrolidinyl(C_1-C_6)alkyl]carbamoyl [e.g. N-{2-(pyrrolidin-1-yl)ethyl}carbamoyl, etc.],
wherein said heterocyclic group may be substituted by suitable substituent(s) such as oxo, carboxy, protected carboxy as mentioned above and carbamoyl, for example, oxopyrrolidinyl substituted by carboxy, C_1-C_6 alkoxycarbonyl or carbamoyl [e.g. 2-oxo-5-carboxypyrrolidinyl, 2-oxo-5-ethoxycarbonylpyrrolidinyl, 2-oxo-5-carbamoylpyrrolidinyl, etc.);
-(C_3-C_7)cycloalkylcarbamoyl (e.g. cyclohexylcarbamoyl, etc.),
-carbamoyl substituted by amino or di(C_1-C_6)alkylamino [e.g. N-aminocarbamoyl, N-(dimethylamino)carbamoyl, etc.],
-N-(optionally substituted heterocyclic)carbamoyl wherein the heterocyclic moiety being thiazolyl, 1,2-thiazolyl, thiadiazolyl, benzothiazolyl, benzothiadiazolyl, morpholinyl, [e.g. thiazolylcarbamoyl, benzothiazolylcarbamoyl and morpholinylcarbamoyl, etc.],.
each of said heterocyclic group may be substituted by lower alkyl, (e.g. methylthiadiazolyl, etc.),
-C_3-C_{10} alkyleneaminocarbonyl (e.g. pyrrolidin-1-ylcarbonyl, hexahydro-1H-azepin-1-ylcarbonyl, etc.),

-C_3-C_6 alkyleneaminocarbonyl substituted by carboxy or protected carboxy such as C_1-C_6 alkoxycarbonyl [e.g. 2-carboxypyrrolidin-1-ylcarbonyl, 2-(methoxycarbonyl)pyrrolidin-1-ylcarbonyl, 2-(ethoxycarbonyl)pyrrolidin-1-ylcarbonyl, etc.],
-C_3-C_6 alkyleneaminocarbonyl wherein said C_3-C_6 alkylene being interrupted by oxygen (e.g. morpholinocarbonyl, etc.),
-C_1-C_6 alkylsulfonylcarbamoyl (e.g. methylsulfonylcarbamoyl, etc.),
-C_6-C_{10}arylsulfonylcarbamoyl (e.g. benzenesulfonylcarbamoyl, etc.), and the like.

Suitable "optionally substituted heterocyclic(C_1-C_6)alkyl" means aforementioned C_1-C_6 alkyl, which is substituted by saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as an oxygen, sulfur, nitrogen atom and the like, as defined below.

The heterocyclic moiety is :

-unsaturated 3 to 8-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, and its N-oxide, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), dihydrotriazinyl (e.g., 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), etc.;
-saturated 3 to 8-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom (s), for example, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, pyrazolidinyl, piperazinyl, etc;
-unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), dihydrotriazolopyridazinyl, etc.;
-unsaturated 3 to 8-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl, (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;
-saturated 3 to 8-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom (s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, etc.;
-unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;
-unsaturated 3 to 8-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 2 sulfur atom (s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, 1,2-thiazolyl, thiazolinyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl), etc.;
-saturated 3 to 8-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 2 sulfur atom (s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;
-unsaturated 3 to 8-membered, preferably 5 or 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.;
-unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc. and the like;

wherein said heterocyclic group may be substituted by one or more, preferably one or two suitable substituent (s) selected from:

-hydroxy;
-protected hydroxy, in which the hydroxy group is protected by a conventional hydroxy-protective group such as acyl as mentioned above, tri(C_1-C_6)alkylsilyloxy (e.g. t-butyldimethylsilyloxy, etc.), etc.;
-halogen (e.g. chlorine, bromine, iodine or fluorine);
-C_1-C_6 alkoxy, which may be straight or branched one alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, hexyloxy, etc., more preferably C_1-C_4 alkoxy (e.g. methoxy, etc.);
-C_1-C_6 alkyl as mentioned above, more preferably C_1-C_4 alkyl (e.g. methyl, etc.); amino; nitro; cyano.

And further when said heterocyclic group has imino-moiety(ies) in its ring, the imino-moiety(ies) may be substituted by suitable substituent(s) such as;

-C_1-C_6 alkyl as mentioned above (e.g. methyl, ethyl, propyl, isobutyl, etc.);
-imino-protective group as mentioned below, more preferably C_1-C_6 alkanoyl oxycarbonyl (e.g. formyl, etc.), arenesulfonyl (e.g. tosyl, etc.); and the like.

Preferable example of "optionally substituted heterocyclic(C_1-C_6)alkyl "thus defined may be :

- C_1-C_6 alkyl substituted by unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom (s), such as pyridyl(C_1-C_6)alkyl, imidazolyl(C_1-C_6)alkyl, etc.;
- C_1-C_6 alkyl substituted by unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s), such as indolyl(C_1-C_6)alkyl, etc.;
- C_1-C_6 alkyl substituted by unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 2 sulfur atom (s) and 1 to 3 nitrogen atom(s) such as thiazolyl(C_1-C_6)alkyl, etc.; and the like,

wherein said heterocyclic group may be substituted by suitable substituent(s) selected from C_1-C_6 alkyl (e.g. methyl, ethyl, propyl, isobutyl, etc.), C_1-C_6 alkanoyl (e.g. formyl, etc.), (C_6-C_{10})arenesulfonyl (e.g. tosyl, etc.), and the like.

More preferable example may be :

- pyridyl(C_1-C_6)alkyl [e.g. 2-(or 3- or 4-)pyridylmethyl, etc.],
- imidazolyl(C_1-C_6)alkyl [e.g. imidazol-1(or 3)-yl methyl, etc.],
- indolyl(C_1-C_6)alkyl [e.g. indol-3-ylmethyl, etc.],
- thiazolyl(C_1-C_6)alkyl [e.g. thiazol-3-ylmethyl, etc.],
- N-arenesulfonylimidazolyl(lower)alkyl (e.g. 1-tosylimidazol-3-ylmethyl, etc.),
- N-(C_1-C_6)alkanoylindolyl(C_1-C_6)alkyl (e.g. N-formylindol-3-ylmethyl, etc.), and
- N-(C_1-C_6)alkylindoyl(C_1-C_6)alkyl [e.g. N-methyl(or ethyl or propyl or isobutyl)indol-3-ylmethyl, etc.] for R^3; and
- pyridyl(C_1-C_6)alkyl (e.g. 2-pyridylmethyl, etc.),
- imidazolyl(C_1-C_6)alkyl [e.g. imidazol-1(or 3)-ylmethyl, etc.], and
- N-arenesulfonylimidazolyl(C_1-C_6)alkyl (e.g. 1-tosylimidazol-3-ylmethyl, etc.) for R^2,

and the most preferred one may be :

-indolyl(C_1-C_6)alkyl, N-(C_1-C_6)alkanoylindolyl(C_1-C_6)alkyl and N-(C_1-C_6)alkylindolyl(C_1-C_6)alkyl for R^3, and -pyridyl(C_1-C_6)alkyl and imidazolyl(C_1-C_6)alkyl for R^2.

Suitable C_6-C_{10} ar(C_1-C_6)alkyl may include phenyl(C_1-C_6)alkyl (e.g. benzyl, phenethyl, etc.), tolyl(C_1-C_6)alkyl, xylyl (C_1-C_6)alkyl, naphthyl(C_1-C_6)alkyl (e.g. naphthylmethyl, etc.), and the like, wherein said C_6-C_{10}ar(C_1-C_6)alkyl may be substituted by suitable substituent(s) selected from those mentioned in the explanation of "optionally substituted heterocyclic(C_1-C_6)alkyl" as mentioned above.

Preferable example of optionally substituted C_6-C_{10}ar(C_1-C_6)alkyl may be phenyl(C_1-C_6)alkyl and naphthyl(C_1-C_6)alkyl, and the most preferable one may be benzyl and naphthylmethyl for R^2, and benzyl for R^3.

Suitable "C_1-C_6 alkylimino" means imino group substituted by aforementioned C_1-C_6 alkyl, in which the most preferable example may be methylimino.

Suitable "cyclo(C_3-C_6)alkyl(C_1-C_6)alkyl" means aforementioned C_1-C_6 alkyl which is substituted by C_3-C_7 cyclo (lower)alkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like, wherein more preferable example may be C_4-C_6 cyclo(C_1-C_6)alkyl and the most preferable one may be cyclohexylmethyl.

Suitable "optionally substituted C_1-C_6 alkyl" may include aforementioned C_1-C_6 alkyl (e.g. methyl, ethyl, isopropyl, butyl, isobutyl, etc.) which is optionally substituted by suitable substituent(s) such as optionally substituted heterocyclic group as mentioned below (e.g. pyridyl, thiazolyl, imidazolyl, N-tosylimidazolyl, etc.); C_6-C_{10} aryl as mentioned below (e.g. phenyl, naphthyl, etc.); amino; protected amino as mentioned below (e.g. benzyloxycarbonylamino, etc.); carboxy; protected carboxy as mentioned above (e.g. benzyloxycarbonyl, etc.); and the like.

Preferable example of "optionally substituted C_1-C_6 alkyl "thus defined may be :

- C_1-C_6 alkyl (e.g. isopropyl, isobutyl, etc.),
- pyridyl(C_1-C_6)alkyl [e.g. 2-(or 3- or 4-)pyridylmethyl, 2-(2-pyridyl)ethyl, etc.],
- thiazolyl(C_1-C_6)alkyl [e.g. 3-thiazolylmethyl, etc.],
- imidazolyl(C_1-C_6)alkyl [e.g. 2-(or 3-)imidazolylmethyl, etc.],
- N-protected imidazolyl(C_1-C_6)alkyl such as N-(arenesulfonyl)imidazolyl(C_1-C_6)alkyl [e.g. N-tosyl-2-(or 3-)imidazolylmethyl, etc.],
- C_6-C_{10} ar(C_1-C_6)alkyl such as phenyl(C_1-C_6)alkyl (e.g. benzyl, naphthylmethyl, etc.),
- amino(C_1-C_6)alkyl (e.g. 4-aminobutyl, etc.),
- protected amino(C_1-C_6)alkyl such as C_6-C_{10} ar(C_1-C_6)alkoxycarbonyl [e.g. 4-(benzyloxycarbonylamino)butyl, etc.],
- carboxy(C_1-C_6)alkyl (e.g. carboxymethyl, 2-carboxyethyl, etc.),
- protected carboxy(C_1-C_6)alkyl such as C_6-C_{10} ar(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl (e.g. benzyloxycarbonylme-

thyl, 2-benzyloxycarbonylethyl, etc.), and the like.

The most preferable example of "optionally substituted C_1-C_6 alkyl" thus defined may be :

- isopropyl, isobutyl,
- 2-(or 3- or 4-)pyridylmethyl, 2-(2-pyridyl)ethyl, 3-thiazolylmethyl, 2-(or 3-)imidazolylmethyl,
- N-tosyl-2-(or 3-)imidazolylmethyl,
- benzyl, naphthylmethyl,
- 4-aminobutyl, 4-(benzyloxycarbonylamino)butyl,
- carboxymethyl, 2-carboxyethyl,
- benzyloxycarbonylmethyl and 2-benzyloxycarbonylethyl for R^4; and
- 2-pyridylmethyl and 2-(2-pyridyl)ethyl for R^6.

Suitable "optionally substituted heterocyclic group" may include the same heterocyclic moiety as mentioned before such as pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, and its N-oxide, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e. g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), dihydrotriazinyl (e.g. 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), thiazolyl, 1,2-thiazolyl, thiazolinyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl), and the like,
wherein said heterocyclic group is optionally substituted by the same substituent(s) mentioned therein such as imino-protective group (e.g. arenesulfonyl, etc.).

Suitable "aryl" may include C_6-C_{10} aryl such as phenyl, tolyl, xylyl, cumenyl, naphthyl, and the like, in which more preferable example may be phenyl and naphthyl.

Suitable amino- or imino protective group for protected amino or protected imino may include acyl as mentioned above, in which more preferable example may be C_1-C_6 alkanoyl, (C_6-C_{10})ar(C_1-C_6)alkoxycarbonyl and (C_6-C_{10}) arenesulfonyl, and the most preferable one may be benzyloxycarbonyl.

Suitable "imino containing heterocyclic(C_1-C_6)alkyl optionally substituted by suitable substituent(s)" means those given for "optionally substituted heterocyclic(C_1-C_6)alkyl" mentioned above, in which the heterocyclic ring contains an imino group (-NH-), such as indolyl(C_1-C_6)alkyl, imidazolyl(C_1-C_6)alkyl, and the like.

Suitable "protected imino containing heterocyclic(C_1-C_6)alkyl optionally substituted by suitable substituent(s)" means aforementioned "imino containing heterocyclic(C_1-C_6)alkyl optionally substituted by suitable substituent(s)", in which the imino group is protected by a conventional imino-protective group as mentioned below.

"Acyl substituted by a protected amino group" means the acyl as explained above which is substituted by the protected amino as mentioned above.

"Acyl substituted by an amino group" means the acyl as explained above which is substituted by amino group.

Suitable "imino-protective group" may include conventional ones used in the peptide chemistry such as those given for the amino-protective group in the protected amino.

The preferred embodiments of each definition may be as follows.

R^1 is carbamoyl, or saturated or unsaturated, acyclic or cyclic aliphatic acyl optionally substituted by aromatic or heterocyclic group(s), aromatic acyl, or heterocyclic acyl, each of which is derived from an organic carboxylic, an organic carbonic, an organic sulfonic or an organic carbamic acyl, for instance:

C_1-C_6 alkanoyl (e.g. acetyl, propionyl, 3,3-dimethylbutyryl, pivaloyl, 4-methylpentanoyl, etc.);

amino(C_1-C_6)alkanoyl (e.g. 2-amino-3-methylpentanoyl, etc.);

protected amino(C_1-C_6)alkanoyl, for example, acylamino(C_1-C_6)alkanoyl such as C_1-C_6 alkoxycarbonylamino(C_1-C_6)alkanoyl (e.g. 2-tert-butoxycarbonylamino-3-methylpentanoyl, etc.), C_3-C_7cycloalkylureido(C_1-C_6)alkanoyl (e.g. 2-(3-cyclohexylureido)-3-methylpentanoyl, etc.);

C_1-C_6 alkoxycarbonyl (e.g. tert-butoxycarbonyl, etc.);

C_3-C_7cycloalkyl(C_1-C_6)alkanoyl (e.g. cyclohexylacetyl, etc.);

C_3-C_7cycloalkylcarbonyl (e.g. cyclohexylcarbonyl, etc.);

C_3-C_7cycloalkyloxycarbonyl (e.g. cyclohexyloxycarbonyl, etc.);

aroyl such as C_6-C_{10}aroyl (e.g. benzoyl, 1- or 2-naphthoyl, etc.);

ar(C_1-C_6)alkanoyl such as C_6-C_{10}ar(C_1-C_6)alkanoyl (e.g. phenylacetyl, 1- or 2-naphthylacetyl, 3-phenylpropionyl, etc.);

amino-substituted ar(C_1-C_6)alkanoyl, for example, amino-substituted (C_6-C_{10})ar(C_1-C_6)alkanoyl such as amino-substituted phenyl(C_1-C_6)alkanoyl (e.g. 2-amino-2-phenylacetyl, etc.);

protected amino-substituted ar(C_1-C_6)alkanoyl, for example, acylamino-substituted (C_6-C_{10})ar(C_1-C_6)alkanoyl such as C_1-C_6 alkoxycarbonylamino-substituted phenyl(C_1-C_6)alkanoyl (e.g. 2-(4-tert-butoxycarbonylaminophenyl)acetyl, 2-tert-butoxycarbonylamino-2-phenylacetyl, etc.);

haloar(C_1-C_6)alkanoyl, for example, halo(C_6-C_{10})ar-(lower)alkanoyl such as halophenyl(C_1-C_6)alkanoyl (e.g. (2-chlorophenyl)acetyl, etc.);

ar(C_1-C_6)alkenoyl, for example, C_6-C_{10}ar(C_1-C_6)-alkenoyl such as phenyl(C_1-C_6)alkenoyl (e.g. cinnamoyl, etc.);

arylglyoxyloyl such as C_6-C_{10}arylglyoxyloyl (e.g. phenylglyoxyloyl, etc.);

ar(C_1-C_6)alkylglyoxyloyl such as C_6-C_{10}ar(C_1-C_6)alkylglyoxyloyl (e.g. benzylglyoxyloyl, etc.);

pyridylcarbonyl (e.g. 2- or 3- or 4-pyridylcarbonyl, etc.);

tetrahydropyridylcarbonyl (e.g. 1,2,3,6-tetrahydropyridin-1-ylcarbonyl, etc.);

tetrahydroquinolylcarbonyl (e.g. 1,2,3,4-tetrahydroquinolin-1-ylcarbonyl, etc.);

tetrahydroisoquinolylcarbonyl (e.g. 1,2,3,4-tetrahydroquinolin-2-ylcarbonyl, etc.);

morpholinylcarbonyl (e.g. morpholinocarbonyl, etc.);

thiomorpholinylcarbonyl (e.g. thiomorpholinocarbonyl, etc.);

indolylcarbonyl (e.g. 2-indolylcarbonyl, etc.);

piperazinylcarbonyl substituted by one to three substituents selected from oxo and C_1-C_6 alkyl (e.g. 4-methyl-2-(1-methylpropyl)-3-oxopiperazin-1-yl-carbonyl, etc.);

pyridyl(C_1-C_6)alkanoyl (e.g. 2- or 3- or 4-pyridylacetyl, etc.);

morpholinylcarbonyl(C_1-C_6)alkanoyl (e.g. 3-(morpholinocarbonyl)propionyl, etc.);

ar(C_1-C_6)alkylsulfonyl, for example, C_6-C_{10}ar(C_1-C_6)alkylsulfonyl such as phenyl(C_1-C_6)alkylsulfonyl (e.g. benzylsulfonyl, etc.);

N- or N,N-di(C_1-C_6 or C_7-C_{12})alkylcarbamoyl such as N- or N,N-di(C_1-C_{10})alkylcarbamoyl (e.g. isopropylcarbamoyl, 2-methylbutylcarbamoyl, heptylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, diisopropylcarbamoyl, dibutylcarbamoyl, diisobutylcarbamoyl, etc.);

hydroxy(C_1-C_6)alkylcarbamoyl (e.g. 1-hydroxymethyl-3-methylbutylcarbamoyl, etc.);

carboxy(C_1-C_6)alkylcarbamoyl (e.g. 1-carboxy-2-methylbutylcarbamoyl, etc.);

protected carboxy(C_1-C_6)alkylcarbamoyl, for example, esterified carboxy(C_1-C_6)alkylcarbamoyl such as lower alkoxycarbonyl(C_1-C_6)alkylcarbamoyl (e.g. 1-methoxycarbonyl-2-methylbutylcarbamoyl, etc.);

carbamoyl(C_1-C_6)alkylcarbamoyl (e.g. 1-carbamoyl-2-methylbutylcarbamoyl, etc.);

[N- or N,N-di(C_1-C_6)alkylcarbamoyl](C_1-C_6)alkylcarbamoyl (e.g. 1-isopropylcarbamoyl-2-methylbutylcarbamoyl, dimethylcarbamoylmethylcarbamoyl, 1-(dimethylcarbamoyl)ethylcarbamoyl, 2-(dimethylcarbamoyl)ethylcarbamoyl, 1-(dimethylcarbamoyl)-2-methylpropylcarbamoyl, 1-(dimethylcarbamoyl)-2,2-dimethylpropylcarbamoyl, 1-(dimethylcarbamoyl)-2-methylbutylcarbamoyl, 1-(dimethylcarbamoyl)-3-methylbutylcarbamoyl, 1-(diethylcarbamoyl)-2-methylbutylcarbamoyl, 1-(dimethylcarbamoyl)pentylcarbamoyl, etc.);

N-C_1-C_6 alkyl-N-[hydroxy(C_1-C_6)alkyl]carbamoyl (e.g. N-(2-hydroxyethyl)-N-methylcarbamoyl, etc.);

N-C_1-C_6 alkyl-N-[di(C_1-C_6)alkylcarbamoyl(C_1-C_6)-alkyl]carbamoyl (e.g. N-(1-dimethylcarbamoyl-2-methylbutyl)-N-methylcarbamoyl, N-(1-dimethylcarbamoyl-3-methylbutyl)-N-methylcarbamoyl, etc.);

C_3-C_6 or C_7-C_{12} alkyleneaminocarbonyl such as C_3-C_{10}alkyleneaminocarbonyl (e.g. pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, 3,5- or 2,6-dimethylpiperidin-1-ylcarbonyl, hexahydro-1H-azepin-1-ylcarbonyl, octahydroazocin-1-ylcarbonyl, etc.);

di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyleneaminocarbonyl (e.g. 2-(dimethylcarbamoyl)pyrrolidin-1-ylcarbonyl, 4-(dimethylcarbamoyl)piperidin-1-ylcarbonyl, etc.);

N-C_1-C_6 alkyl-N-(C_3-C_7)cycloalkylcarbamoyl (e.g. N-cyclohexyl-N-methylcarbamoyl, etc.);

mono- or di(C_3-C_7)cycloalkylcarbamoyl (e.g. cyclohexylcarbamoyl, dicyclohexylcarbamoyl, etc.);

hydroxy- or di(C_1-C_6)alkylcarbamoyl- or di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl-substituted (C_3-C_7)cycloalkylcarbamoyl (e.g. 4-hydroxycyclohexylcarbamoyl, 1- or 4-(dimethylcarbamoyl)cyclohexylcarbamoyl, 1- or 4-(dimethylcarbamoylmethyl)cyclohexylcarbamoyl, etc.);

C_3-C_7cycloalkyl(C_1-C_6)alkylcarbamoyl (e.g. cyclohexylmethylcarbamoyl, etc.);

di(C_1-C_6)alkylcarbayoyl-substituted C_3-C_7cycloalkyl(C_1-C_6)alkylcarbamoyl (e.g. [1-cyclohexyl-1-(dimethylcarbamoyl)methyl]carbamoyl, etc.);

di(C_1-C_6)alkylcarbamoyl-substituted ar(C_1-C_6)alkylcarbamoyl such as di(C_1-C_6)alkylcarbamoyl-substituted phenyl(C_1-C_6)alkylcarbamoyl (e.g. [1-phenyl-1-(dimethylcarbamoyl)methyl]carbamoyl, etc.);

arylcarbamoyl, preferably C_6-C_{10}arylcarbamoyl, in which the aryl group may be substituted by one to three substituents selected from halogen, C_1-C_6 alkyl and C_1-C_6 alkoxy (e.g. phenylcarbamoyl, 2- or 3- or 4-chlorophenylcarbamoyl, 4-tolylcarbamoyl, 4-methoxyphenylcarbamoyl, etc.);

pyridylcarbamoyl (e.g. 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, etc.);

N-protected piperidylcarbonyl, for example, N-acylpireridylcarbonyl such as N-C_1-C_6 alkoxycarbonylpiperidylcarbonyl (e.g. 1-ethoxycarbonylpiperidin-4-ylcarbonyl, etc.);

morpholinyl(C_1-C_6)alkylcarbamoyl (e.g. 2-(morpholino)ethylcarbamoyl, etc.);

C_1-C_6 alkanoylcarbazoyl (e.g. 3-isobutyrylcarbazoyl, etc.);

C_3-C_6 alkyleneaminocarbamoyl (e.g. piperidin-1-yl-carbamoyl, etc.);

N-(C_3-C_7)cycloalkylcarbamoyl(C_1-C_6)alkylcarbamoyl (e.g. 1-cyclohexylcarbamoyl-2-methylbutylcarbamoyl, etc.);

C_3-C_6 alkyleneaminocarbonyl(C_1-C_6)alkylcarbamoyl (e.g. 1-(piperidin-1-ylcarbonyl)-2-methylbutylcarbamoyl,
etc.);

pyridyl(C_1-C_6)alkylcarbamoyl (e.g. 2-pyridylmethylcarbamoyl, etc.); or

oxo-substituted hexahydroazepinylcarbamoyl (e.g. 2-oxo-hexahydro-1H-azepin-3-ylcarbamoyl, etc.);

particularly,

N,N-di(C_1-C_6)alkylcarbamoyl;

mono- or di(C_3-C_7)cycloalkylcarbamoyl;

N-C_1-C_6 alkyl-N-(C_3-C_7)cycloalkylcarbamoyl;

N-C_1-C_6 alkyl-N-[di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl]carbamoyl;

C_6-C_{10}arylcarbamoyl;

C_3-C_6 or C_7-C_{12} alkyleneaminocarbonyl such as C_3-C_{10}alkyleneaminocarbonyl; or

N-C_1-C_6 alkyl-N-[hydroxy(C_1-C_6)alkyl]carbamoyl;

R^2 is C_1-C_6 alkyl (e.g. butyl, isobutyl, 1-methylpropyl, 2,2-dimethylpropyl, etc.);
particularly, isobutyl;

R^3 is indolyl(C_1-C_6)alkyl (e.g. 3-indolylmethyl, etc.);

N-(C_1-C_6)alkylindolyl(C_1-C_6)alkyl (e.g. 1-methyl-3-indolylmethyl, 1-ethyl-3-indolylmethyl, 1-propyl-3-indolylmethyl, 1-isobutyl-3-indolylmethyl, etc.);

N-acylindolyl(C_1-C_6)alkyl such as N-(C_1-C_6) alkanoylindolyl(C_1-C_6)alkyl (e.g. 1-formyl-3-indolylmethyl, etc.); or

C_6-C_{10}ar(C_1-C_6)alkyl (e.g. benzyl, 1- or 2-naphthylmethyl, etc.);

particularly,
N-(C_1-C_6)alkylindolyl(lower)alkyl such as 1-methyl-3-indolylmethyl;

R^4 is, C_1-C_6 lower alkyl (e.g. isopropyl, isobutyl, etc.);

amino(C_1-C_6)alkyl (e.g. 4-aminobutyl, etc.);

protected amino(C_1-C_6)alkyl, for example, acylamino(C_1-C_6)alkyl such as mono- or di or triphenyl(C_1-C_6) alkoxycarbonylamino(C_1-C_6)alkyl (e.g. 4-benzyloxycarbonylaminobutyl, etc.);

carboxy(C_1-C_6)alkyl (e.g. carboxymethyl, 2-carboxyethyl, etc.);

protected carboxy(C_1-C_6)alkyl, for example, esterified carboxy(C_1-C_6)alkyl such as mono- or di or triphenyl(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl (e.g. benzyloxycarbonylmethyl, 2-benzyloxycarbonylethyl, etc.);

ar(C_1-C_6)alkyl such as C_6-C_{10}ar(C_1-C_6)alkyl (e.g. benzyl, 1- or 2-naphthyl, etc.);

pyridyl(C_1-C_6)alkyl (e.g. 2- or 3- or 4-pyridylmethyl, etc.);

imidazolyl(C_1-C_6)alkyl (e.g. 1H-4-imidazolylmethyl, etc.); or

thiazolyl(C_1-C_6)alkyl (e.g. 4-thiazolylmethyl, etc.);

particularly,

C_6-C_{10}ar(C_1-C_6)alkyl such as benzyl; or

pyridyl(C_1-C_6)alkyl such as 2-pyridylmethyl;

R^5 is carboxy;
esterified carboxy selected from :

C_1-C_6 alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, etc.),

C_6-C_{10} ar(C_1-C_6)alkoxycarbonyl such as mono or di or triphenyl(C_1-C_6)alkoxycarbonyl (e.g. benzyloxycarbonyl, etc.),

C_6-C_{10} aroyl(C_1-C_6)alkoxycarbonyl such as benzoyl(C_1-C_6)alkoxycarbonyl (e.g. phenacyl, etc.);

amidated carboxy selected from :

carbamoyl,

N- or N,N-di(C_1-C_6)alkylcarbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl etc.),

C_1-C_6 alkylcarbamoyl substituted by one or two substituents selected from carboxy and protected carboxy (preferably, esterified carboxy, more preferably, C_1-C_6 alkoxycarbonyl, mono or di or triphenyl(C_1-C_6) alkoxycarbonyl or benzoyl(C_1-C_6)-alkoxycarbonyl) (e.g. carboxymethylcarbamoyl, 1- or 2-carboxyethylcarbamoyl, 4-carboxybutylcarbamol, 5-carboxypentylcarbamoyl, 1-carboxy-2-methylpropylcarbamoyl, 1-carboxy-3-methylbutylcarbamoyl, 1,2-dicarboxyethylcarbamoyl, benzyloxycarbonylmethylcarbamoyl, 2-benzyloxycarbonylethylcarbamoyl, 1- or 2-phenacyloxycarbonylethylcarbamoyl, 4-phenacyloxycarbonylbutylcarbamoyl, 5-phenacyloxycarbonylpentylcarbamoyl, 1-methoxycarbonyl-2-methylpropylcarbamoyl, 1-methoxycarbonyl-3-methylbutylcarbamoyl, 1,2-bis(methoxycarbonyl)ethylcarbamoyl, etc.),

N-(C_1-C_6)alkyl-N-[carboxy- or protected carboxy (preferably, esterified carboxy, more preferably C_1-C_6 alkoxycarbonyl)(C_1-C_6)alkyl]carbamoyl (e.g. N-methyl-N-(carboxymethyl)carbamoyl, N-methyl-N-(methoxycarbonylmethyl)carbamoyl, etc.),

C_6-C_{10} ar(C_1-C_6)alkylcarbamoyl, for example, C_6-C_{10}ar(C_1-C_6)alkylcarbamoyl such as phenyl(C_1-C_6) alkylcarbamoyl (e.g. benzylcarbamoyl, etc.),

carboxy- or protected carboxy (preferably, esterified carboxy)-substituted C_6-C_{10}ar(C_1-C_6)alkylcarbamoyl such as carboxy- or C_1-C_6 alkoxycarbonyl-substituted phenyl(C_1-C_6)alkylcarbamoyl (e.g. 1-carboxy-2-phenylethylcarbamoyl, 1-ethoxycarbonyl-2-phenylethylcarbamoyl, etc.),

C_3-C_7cycloalkylcarbamoyl (e.g. cyclohexylcarbamoyl, etc.),

N-[carboxy- or protected carboxy-substituted C_3-C_7cycloalkyl(C_1-C_6)alkyl]carbamoyl, for example, [carboxy(C_3-C_7)cycloalkyl(C_1-C_6)alkyl]carbamoyl (e.g. 4-carboxycyclohexylmethylcarbamoyl, etc.), esterified carboxy-substituted C_3-C_7cycloalkyl(C_1-C_6)alkyl]carbamoyl such as C_1-C_6 alkoxycarbonyl(C_3-C_7)cycloalkyl(C_1-C_6)alkyl]carbamoyl (e.g. 4-(ethoxycarbonyl)cyclohexylmethylcarbamoyl, etc.),

C_1-C_6 alkylsulfonylcarbamoyl (e.g. methylsulfonylcarbamoyl, etc.), arylsulfonylcarbamoyl, for example, C_6-C_{10}arylsulfonylcarbamoyl (e.g. phenylsulfonylcarbamoyl, etc.),

carboxy- or protected carboxy (preferably, esterified carboxy)-substituted pyridyl(C_1-C_6)alkylcarbamoyl such as carboxy- or C_1-C_6 alkoxycarbonyl-substituted pyridyl(C_1-C_6)alkylcarbamoyl (e.g. 1-carboxy-2-(2-pyridyl)ethylcarbamoyl, 1-ethoxycarbonyl-2-(2-pyridyl)ethylcarbamoyl, etc.)

C_3-C_6 alkyleneaminocarbonyl (e.g. pyrrolidin-1-yl-carbonyl, piperidin-1-ylcarbonyl, etc.),

C_3-C_6 alkyleneaminocarbonyl substituted by carboxy or protected carboxy (preferably, esterified carboxy, more preferably, C_1-C_6 alkoxycarbonyl) (e.g. 2-carboxypyrrolidin-1-ylcarbonyl, 2-methoxycarbonylpyrrolidin-1-ylcarbonyl, etc.),

[C_3-C_6 alkyleneamino(C_1-C_6)alkyl]carbamoyl substituted by one to two substituents selected from carboxy, protected carboxy (preferably, esterified carboxy, more preferably, C_1-C_6 alkoxycarbonyl) and carbamoyl (e.g. 2-(2-carboxy-5-oxopyrrolidin-1-yl)ethylcarbamoyl, 2-(2-ethoxycarbonyl-5-oxopyrrolidin-1-yl) ethylcarbamoyl, 2-(2-carbamoyl-5-oxopyrrolidin-1-yl)ethylcarbamoyl, etc.),

morpholinocarbonyl,

morpholinylcarbamoyl (e.g. morpholinocarbamoyl, etc.),

pyridylcarbamoyl (e.g. 2-pyridylcarbamoyl, etc.),

thiazolylcarbamoyl (e.g. 2-thiazolylcarbamoyl, etc.),

C_1-C_6 alkylthiadiazolylcarbamoyl such as 5-(C_1-C_6)alkyl-1,3,4-thiadiazolylcarbamoyl (e.g. 5-methyl-1,3,4-thiadiazolylcarbamoyl, etc.),

benzothiazolylcarbamoyl (e.g. 2-benzothiazolylcarbamoyl, etc.),

morpholinyl(C_1-C_6)alkylcarbamoyl (e.g. 2-morpholinoethylcarbamoyl, etc.),

pyridyl(C_1-C_6)alkylcarbonyl (e.g. 2-pyridylmethylcarbonyl, etc.),

carbazoyl,

di(C_1-C_6)alkylcarbazoyl (e.g. 3,3-dimethylcarbazoyl, etc.);

carboxy(C_1-C_6)alkyl (e.g. carboxymethyl, 2-carboxyethyl, 3-carboxypropyl, 4-carboxybutyl, etc.); or

protected carboxy(C_1-C_6)alkyl, for example, esterified carboxy(C_1-C_6)alkyl such as lower alkoxycarbonyl (C_1-C_6)alkyl (e.g. methoxycarbonylmethyl, 2-methoxycarbonylethyl, 3-methoxycarbonylpropyl, 4-methoxycarbonylbutyl, etc.), aroyl(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl (e.g. phenacyloxycarbonylmethyl, 2-phenacyloxycarbonylethyl, 3-phenacyloxycarbonylpropyl, 4-phenacyloxycarbonylbutyl, etc.);

particularly,

carboxy;

C_1-C_6 alkoxycarbonyl; or

carbamoyl;

N- or N,N-di(C_1-C_6)alkylcarbamoyl;

R^6 is hydrogen; or

pyridyl(C_1-C_6)alkyl (e.g. 2-pyridylmethyl, 2-(2-pyridyl)ethyl, etc.);

particularly, hydrogen;

R^7 is hydrogen; or

C_1-C_6 alkyl (e.g. methyl, etc.);

particularly, hydrogen; and

A is C_1-C_6 alkylene (e.g. methylene, etc.);

-O-; -NH-; or

C_1-C_6 alkylimino (e.g. methylimino, etc.);

particularly, methylene or -NH-.

The processes for preparing the object compound (I) are explained in detail in the following.

Process 1

The object compound (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the carboxy group, or a salt thereof with the compound (III) or its reactive derivative at the amino group, or a salt thereof.

Suitable reactive derivative at the amino group of the compound (III) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (III) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (III) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (III) with phosphorus trichloride or phosgene, and the like.

Suitable salts of the compound (III) and its reactive derivative can be referred to the acid addition salts as exemplified for the compound (I).

Suitable reactive derivative at the carboxy group of the compound (II) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminiomethyl $[(CH_3)_2\overset{+}{N}=CH-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (II) to be used.

Suitable salts of the compound (II) and its reactive derivative may be a base salt such as an alkali metal salt [e.g. sodium salt, potassium salt, etc.], an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.], an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt N,N'-dibenzylethylenediamine salt, etc.], or the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound (II) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonylbis(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; thionyl chloride; oxalyl chloride; C_1-C_6 alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; N-hydroxybenzotriazole; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(C_1-C_6)alkylamine, pyridine, N-(C_1-C_6)-alkylmorpholine, N,N-di(C_1-C_6)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 2

The object compound (I-b) or a salt thereof can be prepared by reacting the compound (I-a) or its reactive derivative at the amino group, or a salt thereof with the compound (IV) or its reactive derivative at the carboxy group, or a salt thereof.

Suitable salts of the compound (I-a) and its reactive derivative can be referred to the ones as exemplified for the compound (III).

Suitable salts of the compound (IV) and its reactive derivative can be referred to the ones as exemplified for the compound (II).

Suitable salts of the compound (I-b) can be referred to the ones as exemplified for the compound (I).

In case that the acyl of the symbol "R^1" is one derived from carbamic acids, the starting compound (IV) is usually used in a form of isocyanates.

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. reactive derivatives, solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

Process 3

The object compound (I) or a salt thereof can be prepared by reacting the compound (V) or its reactive derivative at the carboxy group, or a salt thereof with the compound (VI) or its reactive derivative at the amino group, or a salt thereof.

Suitable salts of the compound (V) and its reactive derivative can be referred to the ones as exemplified for the compound (II).

Suitable salts of the compound (VI) and its reactive derivatives can be referred to the ones as exemplified for the compounds (I) and (III), respectively.

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. reactive derivatives, solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

Process 4

The object compound (I-d) or a salt thereof can be prepared by subjecting a compound (I-c) or a salt thereof to removal reaction of the carboxy-protective group in R^5_a.

Suitable salts of the compounds (I-c) and (I-d) can be referred to the ones as exemplified for the compound (I).

This reaction is carried out in accordance with a conventional method such as solvolysis including hydrolysis, reduction or the like.

The solvolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, hydrazine, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]-non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, hydrogen fluoride, etc.].

The removal reaction using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like, is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, chloroform, carbon tetrachloride, tetrahydrofuran, N,N-dimethylformamide, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reduction method applicable for the removal reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.],

cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron, etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acid to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to heating.

Process 5

The object compound (I-f) or a salt thereof can be prepared by subjecting the compound (I-f) or a salt thereof to removal reaction of the imino- or amino-protective group(s) in R_a^2.

Suitable salts of the compounds (I-e) and (I-f) can be referred to the ones as exemplified for the compound (I).

This removal reaction can be carried out by a conventional method in the peptide chemistry such as solvolysis, reduction, and the like, the details of which can be referred to those of Process 4.

Process 6

The object compound (I-h) or a salt thereof can be prepared by subjecting the compound (I-g) or a salt thereof to removal reaction of the amino-protective group in R_a^1.

Suitable salts of the compounds (I-g) and (I-h) can be referred to the ones as exemplified for the compound (I).

This removal reaction can be carried out by a conventional method in the peptide chemistry such as solvolysis, reduction, and the like, the details of which can be referred to those of Process 4.

Process 7

The object compound (I-j) or a salt thereof can be prepared by reacting the compound (I-i) or its reactive derivative at the carboxy group, or a salt thereof with an optionally substituted amine, or a salt thereof.

Suitable salts of the compound (I-i) and its reactive derivative can be referred to the ones as exemplified for the compound (II).

Suitable salts of the compound (I-j) can be referred to the ones as exemplified for the compound (I).

Suitable optionally substituted amines means the ones which can form aforementioned amidated carboxy of R_d^5 in the resulting compound (I-j).

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. reactive derivatives, solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

Process 8

The compound (I-g) or a salt thereof can be prepared by acylating the amino group in R_b^1 of the compound (I-h) or a salt thereof.

Suitable salts of the compounds (I-g) and (I-h) may be the same as those for the compound (I).

Suitable acylating agent used in this reaction may be a conventional acylating agent which is capable of introducing the acyl group as mentioned before such as carboxylic acid, carbonic acid, sulfonic acid and their reactive derivative, for example, an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Preferable example of such reactive derivative may include acid chloride, acid bromide, a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, alkyl carbonate (e.g. methyl carbonate, ethyl carbonate, propyl carbonate, etc.), aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.), aromatic carboxylic acid (e.g. benzoic acid, etc.), a symmetrical acid anhydride, an activated acid amide with a heterocyclic compound containing imino function such as imidazole, 4-substituted imidazole, dimethylpyrazole, triazole and tetrazole, an activated ester (e.g. p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyridyl ester, piperidinyl ester, 8-quinolyl thioester, or an ester with a N-hydroxy compound such as N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxybenzotriazole, 1-hy-

droxy-6-chlorobenzotriazole, etc.), and the like.

This reaction can be carried out in the presence of an organic or inorganic base such as alkali metal (e.g. lithium, sodium, potassium, etc.), alkaline earth metal (e.g. calcium, etc.), alkali metal hydride (e.g. sodium hydride, etc.), alkaline earth metal hydride (e.g. calcium hydride, etc.), alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.), alkali metal alkanoic acid (e.g. sodium acetate, etc.), trialkylamine (e.g. triethylamine, etc.), pyridine compound (e.g. pyridine, lutidine, picoline, 4-dimethylaminopyridine, etc.), quinoline, and the like.

In case that the acylating agent is used in a free form or its salt in this reaction, the reaction is preferably carried out in the presence of a condensing agent such as a carbodiimide compound [e.g. N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, etc.], a ketenimine compound (e.g. N,N'-carbonylbis(2-methylimidazole), pentamethyleneketene-N-cyclohexylimine, diphenylketene-N-cyclohexylimine, etc.); an olefinic or acetylenic ether compounds (e.g. ethoxyacetylene, β-chlorovinylethyl ether), a sulfonic acid ester of N-hydroxybenzotriazole derivative [e.g. 1-(4-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole, etc.], a combination of trialkylphosphite or triphenylphosphine and carbon tetrachloride, disulfide or diazenedicarboxylate (e.g. diethyl diazenedicarboxylate, etc.), a phosphorus compound (e.g. ethyl polyphosphate, isopropyl polyphosphate, phosphoryl chloride, phosphorus trichloride, etc.), thionyl chloride, oxalyl chloride, N-ethylbenzisoxazolium salt, N-ethyl-5-phenylisoxazolium-3-sulfonate, a reagent (referred to a so-called "Vilsmeier reagent") formed by the reaction of an amide compound such as N,N-di(C_1-C_6)alkylformamide (e.g. dimethylformamide, etc.), N-methylformamide or the like with a halogen compound such as thionyl chloride, phosphoryl chloride, phosgene or the like.

The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, acetone, dichloromethane, alcohol (e.g. methanol, ethanol, etc.), tetrahydrofuran, pyridine, N,N-dimethylformamide, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to heating.

Process 9

The object compound (I-a) or a salt thereof can be prepared by subjecting the compound (I-b) or a salt thereof to a removal reaction of the acyl group of R^1_c.

This removal reaction can be carried out by a conventional method in the peptide chemistry such as solvolysis, reduction, and the like, the details of which can be referred to those of Process 4.

Process 10

The object compound (I-ℓ) or a salt thereof can be prepared by subjecting a compound (I-k) or a salt thereof to removal reaction of the carboxy-protective group in R^4_c.

Suitable salts of the compound (I-k) and (I-ℓ) can be referred to ones as exemplified for the compound (I).

This removal reaction can be carried out by a conventional method in the peptide chemistry such as solvolysis, reduction, and the like, the details of which can be referred to those of Process 4.

Process 11

The object compound (I-n) or a salt thereof can be prepared by subjecting a compound (I-m) or a salt thereof to removal reaction of the imino-protective group in R^3_a.

Suitable salts of the compound (I-m) and (I-n) can be referred to ones as exemplified for the compound (I).

This removal reaction can be carried out by a conventional method in the peptide chemistry such as solvolysis, reduction, and the like, the details of which can be referred to those of Process 4.

Process 12

The object compound (I-p) or a salt thereof can be prepared by subjecting a compound (I-o) or a salt thereof to removal reaction of the amino or imino-protective group in R^4_a.

Suitable salts of the compound (I-o) and (I-p) can be referred to ones as exemplified for the compound (I).

This removal reaction can be carried out by a conventional method in the peptide chemistry such as solvolysis, reduction, and the like, the details of which can be referred to those of Process 4.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

The object compound (I) can be transformed into its salt in a conventional manner.

The method for preparing the new starting compounds are explained in detail in the following.

Method 1

[Step 1]

The compound (III-a) or a salt thereof can be prepared by reacting the compound (VII) or its reactive derivative at the carboxy group, or a salt thereof with the compound (VI) or its reactive derivative at the amino group, or a salt thereof.

Suitable salts of the compound (VII) and its reactive derivative can be referred to the ones as exemplified for the compound (II).

Suitable salts of the compound (VIII) and its reactive derivative can be referred to the ones as exemplified for the compound (III).

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. reactive derivatives, solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

[Step 2]

The compound (II) or a salt thereof can be prepared by subjecting the compound (III-a) or a salt thereof to a removal reaction of the amino-protective group of R^8 in a conventional manner such as those explained in Process 4.

Method 2

[Step 1]

The compound (IX) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the carboxy group, or a salt thereof with the compound (VIII) or its reactive derivative at the amino group, or a salt thereof.

Suitable salts of the compound (IX) can be referred to the ones as exemplified for the compound (I).

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. reactive derivatives, solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

[Step 2]

The compound (V) or a salt thereof can be prepared by subjecting the compound (IX) or a salt thereof to a removal reaction of the carboxy-protective group of R^9 in a conventional manner such as those explained in Process 4.

It is to be noted that the compound (I) and the other compounds may include one or more stereoisomers due to asymmetric carbon atoms, and all of such isomers and mixture thereof are included within the scope of this invention.

The object compound (I) and a pharmaceutically acceptable salt thereof have endothelin antagonistic activity such as relaxating activity of blood vessel, and the like, and are useful for therapeutical treatment and prevention of endothelin mediated diseases such as hypertension, heart disease such as angina pectoris, cardiomyopathy, myocardial infarction or the like, cerebral stroke such as cerebral arterial spasm, cerebral ischemia, cerebrovascular twitch or the like, late phase cerebral spasm after subarachnoid hemorrhage, asthma such as bronchoconstriction or the like, renal failure such as acute renal failure, renal insufficiency caused by pharmaceuticals (e.g. Cisplatin, Cyclosporins, etc.), peripheral circulatory failure, such as Raynaud'd disease, Buerger's disease, etc, arteriosclerosis, diabetic nephropathy, diabetic retinopathy, shock such as hemorrhagic shock, shock induced by endotoxins, etc, hemangioendothelioma, organopathy after re-perfusion [e.g. after organ and tissue transplantation, percutaneous transluminal coronary angiopathy (PTCA), or percutaneous transluminal coronary recanalization (PTCR), etc.], bloodstream disturbance after an operation, ulcer, irritable bowel syndrome (IBS), dysuria, retinopathy, dysmenorrheal, premature birth such as premature labor, threatened abortion, or the like, glaucoma, re-occlusion after operation of PTCA, and the like.

For therapeutic purpose, the peptide compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, solution, suspension, emulsion, sublingual tablet, suppositories, ointment, aerosol, infusion, ophthalmic solutions, vaginal suppository, and the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound (I) will vary depending upon the age and condition of the patient, in the case of intravenous administration, a daily dose of 0.01 - 100 mg of the active ingredient per kg weight of human being, in the case of intramuscular administration, a daily dose of 0.05 - 100 mg of the same per kg weight of human being, in case of oral administration, a daily dose of 0.1 - 100 mg of the same per kg weight of human being is generally given for the treatment of endothelin-mediated diseases.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of some representative compounds of the compound (I) are shown in the following.

Test 1

Radioligand binding assay :

(1) Test Compounds

a. Compound A [The compound of Example 7-2)]
b. Compound B [The compound of Example 236]
c. Compound C [The compound of Example 264]
d. Compound D [The compound of Example 258]
e. Compound E [The compound of Example 313]

(2) Test Method

(a) Crude receptor membrane preparation :

Porcine aorta was purchased from Pel-Freez Biologicals (U.S.A.) and stored at -80°C until use.

Porcine aorta (50 g) was thawed and dissected free from fatty tissue, minced with scissors and then homogenized with a polytron (Brinkmann PT-20, maximal speed for 3 x 10 sec) in 100 ml buffer (0.25 M sucrose, 10 mM Tris-HCl, 0.1 mM EDTA).

The homogenate was centrifuged at 10,000 g for 20 minutes at 4°C.

The supernatant, containing the plasma membrane fraction, was centrifuged at 100,000 g for 60 minutes at 4°C, and then resultant pellets were referred to as crude membrane fractions.

The pellets were resuspended in 25 ml of binding assay buffer (50 mM Tris-HCl, 100 mM NaCl, 5 mM $MgCl_2$, 1.5 µg/ml phenylmethylsulfonyl fluoride (PMSF), 120 µg/ml bacitracin, 12 µg/ml leupepcin, 6 µg/ml chymostain, 0.1% bovine serum albumin (BSA), pH 7.5).

The aorta membrane fractions were stored at -80°C until use.

(b) ^{125}I-endothelin-1 binding assay :

^{125}I-Endothelin-1 (1.67×10^{-11} M) (Amersham Japan, specific activity : 2000 Ci/m mol) was incubated with 50 µl of aorta membrane preparation in binding assay buffer at room temperature (20-22°C) for 60 minutes in a final volume of 250 µl.

After incubation, the incubation mixture were filtered through Glass-fiber GF/C filter (pretreated with 0.1% polyethylene imine for 3 hours prior to use) using cell harvester (Brandel M-24S). The filters were then washed ten times with a total of 3 ml of the washing buffer (50 mM Tris-HCl, pH 7.5) at 0°C. The filters were counted in a gamma counter (Packard Auto Gamma Model 5650).

(3) Test Results

The results are shown in Table 1.

Table 1 :

Effect on specific binding of ^{125}I-endothelin-1 in porcine aorta membrane	
Test Compound	IC_{50} (M)
A	2.3×10^{-9}
B	3.2×10^{-8}
C	7.6×10^{-9}
D	2.1×10^{-8}

Table 1 : (continued)

Effect on specific binding of ^{125}I-endothelin-1 in porcine aorta membrane	
Test Compound	IC_{50} (M)
E	7.6×10^{-9}

Test 2

Effect on rabbit aorta or contraction response of endothelin :

(1) Test Compound
Test Compound A

(2) Test Method
Thoracic aorta were isolated from freshly killed male albino rabbits (11 weeks old) and cut into 25 mm strips with the intima denuded. After removing fatty tissues, these arterial segments (2 mm width and 25 mm length) were suspended in 25 ml organ chambers filled with Krebs-Ringer solution (113 mM NaCl, 4.8 mM KCl, 2.2 mM $CaCl_2$, 1.2 mM $MgCl_2$, 25 mM $NaHCO_3$, 1.2 mM KH_2PO_4, 5.5 mM glucose) maintained at 37°C and gassed with 95% O_2/5% CO_2.

A preload of 0.5 g was applied after the aorta had been conditioned by application of increasing concentration of KCl. Contractions were measured as an increase in isometric tension.

Test Compound was tested against contractile response of rabbit aorta induced by endothelin (3.2×10^{-9} M). Synthetic endothelin was obtained from Peptide Institute Inc. (Osaka, Japan). Test Compound was added after the full contraction response induced by endothelin.

(3) Test Result
The activity of Test Compound is expressed as the IC_{50} value of maximum contraction response induced by endothelin and shown in Table 2.

Table 2 :

Effect on the contractile responses of rabbit thoracic aorta induced by endothelin	
Test Compound	Inhibition against contraction response of endothelin (IC_{50})
A	2.3×10^{-7} M

Test 3

Effect on endothelin-1-pressor response

(1) Test Compound
Test Compound A

(2) Test Method
Wistar rats, weighing 200 g to 250 g, were anesthetized with ether, and the abdominal aorta was canulated with a polyethylene tube via the femoral artery and vein for blood pressure measurement and intravenous injection of endothelin-1. The animals were allocated to recover for 3 hours and tethered in each cage.

The blood pressure was directly monitored via pressure transducer (PT-200T, made by Nihon Kohden) and were recorded on a pre-writing recorder (CWT685G, made by Nihon Kohden). Pressor response to intravenous injection of endothelin-1 (3.2 µg/kg) was obtained.

This dose produced a sustained pressor response which continued over 1 hour.

The effect of intravenous injection of the Test Compound was studied in rats 20 minutes after starting an intravenous injection of endothelin-1.

(3) Test Result
Potency of the Test Compound in rats was expressed by the following index.

++ : completely antagonized (almost 100%)
+ : moderately antagonized (about 50%)
- : no effect

Test Compound	Dose (mg/kg)	Response
A	10	++

From the results of the above-mentioned biological test, it is clear that compound (I) has endothelin antagonistic activity, therefore are useful for the treatment and prevention of endothelin mediated diseases, for example, hypertension, heart disease such as angina pectoris, cardiomyopathy, myocardial infarction or the like, cerebral stroke such as cerebral arterial spasm, cerebral ischemia, cerebrovascular twitch or the like, late phase cerebral spasm after subarachnoid hemorrhage, asthma such as bronchoconstriction or the like, renal failure such as acute renal failure, renal insufficiency caused by pharmaceuticals (e.g. Cisplatin, Cyclosporins, etc.), or the like.

The following examples are given for purpose of illustrating the present invention in detail.

In these examples, there are employed the following abbreviations in addition to the abbreviations adopted by the IUPAC-IUB.

Ac	acetyl
Boc :	t-butoxycarbonyl
Bu	butyl
Bzl	benzyl
DMF :	dimethylformamide
DMSO :	dimethyl sulfoxide
Et :	ethyl
HOBT :	N-hydroxybenzotriazole
Me :	methyl
NMM :	N-methylmorpholine
Pac :	phenacyl
D-Pya :	D-(2-pyridyl)alanine
D-4Pya :	D-(4-pyridyl)alanine
TFA :	trifluoroacetic acid
TEA :	triethylamine
Ts or Tos :	tosyl
WSCD :	1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide
Z :	benzyloxycarbonyl
DMAP :	dimethylaminopyridine

Preparation 1-1)

To a mixture of Boc-D-Trp(CH_3)-OH (1.59 g), HCl·H-D-Phe-OCH_3 (1.08 g) and HOBT (0.81 g) in DMF (20 ml) was added WSCD (0.93 g) under ice-bath cooling. After being stirred for 2 hours at room temperature, the mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (50 ml). The solution was washed with 0.5N hydrochloric acid (20 ml), water (20 ml), saturated sodium bicarbonate (20 ml) and water (20 ml x 2) successively, dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with ether to give Boc-D-Trp(CH_3)-D-Phe-OCH_3 (1.45 g).

mp : 95-96°C

Rf : 0.83 ($CHCl_3$:MeOH = 9:1)

Preparation 1-2)

A solution of Boc-D-Trp(CH_3)-D-Phe-OCH_3 (1.40 g) in a mixture of anisole (1.4 ml) and TFA (14 ml) was stirred for one hour at 0°C. The mixture was concentrated in vacuo and dissolved in 4N HCl in 1,4-dioxane (10 ml) and the solution was concentrated in vacuo. The residue was triturated with ether to give HCl·H-D-Trp(CH_3)-D-Phe-OCH_3 (1.09 g).

mp : 188-192°C

Rf : 0.51 ($CHCl_3$:MeOH = 9:1)

Preparation 1-3)

Phenylacetyl chloride (5.7 ml) was added dropwise to a mixture of TsOH·H-1-Leu-OBzl (14.15 g) and TEA (12 ml) in dichloromethane (300 ml) under ice-bath cooling. After being stirred for 10 minutes at the same temperature, the mixture was concentrated in vacuo, and the residue was dissolved in ethyl acetate (300 ml). The solution was washed with 1N HCl (100 ml), water (100 ml), 1M aqueous sodium bicarbonate (100 ml), and brine (100 ml x 2), dried over magnesium sulfate and evaporated to give N-phenylacetyl-1-Leu-OBzl (14 g). This product was used in a next step without further purification.

Rf : 0.50 ($CHCl_3$:MeOH = 9:1)

Preparation 1-4)

A solution of N-phenylacetyl-1-Leu-OBzl (14 g) in methanol (140 ml) was hydrogenated over 10% palladium on carbon (1.4 g) at 3 atmospheric pressure of hydrogen for 2 hours. After removal of the catalyst by filtration, the filtrate was concentrated in vacuo. The residue was triturated with diisopropyl ether to give N-phenylacetyl-1-Leu-OH (7.7 g).

mp : 135-136°C

Rf : 0.17 ($CHCl_3$:MeOH = 9:1)

Preparation 2-1)

Boc-D-Trp(CH_3)-D-Phe-OBzl was obtained in 87.2% yield in substantially the same manner as that of Preparation 1-1).

Rf : 0.77 ($CHCl_3$:MeOH= 9:1)

Preparation 2-2)

HCl·H-D-Trp(CH_3)-D-Phe-OBzl was obtained quantitatively in substantially the same manner as that of Preparation 1-2).

mp : 147-150°C

Rf : 0.57 ($CHCl_3$:MeOH = 9:1)

Preparation 3-1)

Boc-1-Leu-OH (1.30 g), HCl·H-D-Trp(CH_3)-OBzl (1.76 g), WSCD (950 mg) and HOBT (827 mg) in DMF (30 ml) was reacted at 5°C overnight in a similar manner to that of Preparation 1-1) to give Boc-1-Leu-D-Trp(CH3)-OBzl (2.48 g).

mp : 124-126°C

Rf : 0.87 ($CHCl_3$:MeOH = 9:1)

Preparation 3-2)

Boc-1-Leu-D-Trp(CH3)-OBzl (2.40 g) in MeOH (50 ml) and water (1 ml) was hydrogenated over 10% palladium on carbon in a similar manner to that of Preparation 1-4) to give Boc-1-Leu-D-Trp(CH_3)-OH (1.95 g).

mp : 64-67°C

Rf 0.57 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Preparation 4-1)

N-Phenylacetyl-1-Leu-D-Trp(CH_3)-OBzl (5.96 g) was obtained from N-phenylacetyl-1-Leu-OH (2.96 g), HCl·H-D-Trp(CH_3)-OBzl (3.9 g), HOBT (1.68 g) and WSCD (1.93 g) in a similar manner to that of Preparation 1-1).

mp : 152-155°C

Rf : 0.72 ($CHCl_3$:MeOH = 9:1)

Preparation 4-2)

To a solution of N-phenylacetyl-1-Leu-D-Trp(CH_3)-OBzl (5.9 g) in a mixture of methanol (60 ml), acetic acid (60

ml) and DMF (100 ml) was added 10% palladium on activated carbon (0.6 g). The mixture was stirred for 5 hours at 3 atmospheric pressure of hydrogen at room temperature. The solution was filtered and the filtrate was concentrated in vacuo. The residue was triturated with ether-ethyl acetate to give N-phenylacetyl-1-Leu-D-Trp(CH_3)-OH (4.69 g).

mp : 76-79°C

Rf : 0.50 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Preparation 5

Boc-D-Trp(CH_3)-OH (6.0 g), D-Pya-OC_2H_5·2HCl (5.54 g), WSCD (3.51 g), HOBT (3.05 g) and TEA (2.09 g) were reacted in DMF (200 ml) in a similar manner to that of Preparation 1-1) to give Boc-D-Trp(CH_3)-D-Pya-OC_2H_5 (6.18 g).

mp : 99-101°C

Rf : 0.67 ($CHCl_3$:MeOH = 9:1)

Preparation 6

Boc-D-Trp(CH_3)-D-Pya-OC_2H_5 (4.50 g), TFA (50 ml) and anisole (5 ml) were reacted in a similar manner to that of Preparation 1-2) to give 2HCl·H-D-Trp(CH_3)-D-Pya-OC_2H_5 (4.15 g).

mp : 81-83°C

Rf : 0.22 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Preparation 7

To a solution of (S)-α-benzyloxycarbonyl-γ-methylbutyl isocyanate (1.50 g) in ethyl acetate (60 ml) was added hexahydro-1H-azepine (722 mg) at room temperature. After being stirred for 30 minutes at the same temperature, the solution was washed with 5% HCl, 1M sodium bicarbonate solution and saturated sodium chloride solution successively, and dried over anhydrous magnesium sulfate. The solution was concentrated in vacuo to give N-(hexahydro-1H-azepin-1-ylcarbonyl)-1-Leucine benzyl ester (2.06 g) as a crystal.

mp : 79-82°C

Rf : 0.64 (n-hexane:EtOAc = 1:1)

Preparation 8

(2S)-2-Amino-3,3-dimethyl-N,N-dimethylbutyramide hydrochloride (0.20 g), (S)-α-benzyloxycarbonyl-γ-methylbutyl isocyanate (0.25 g) and TEA (0.1 ml) were reacted in ethyl acetate (10 ml) in a similar manner to that of Preparation 7 to give N-[(1S)-2,2-dimethyl-1-(N,N-dimethylcarbamoyl)propyl]carbamoyl]-1-Leu-OBzl (0.40 g).

Rf : 0.59 (hexane:EtOAc = 2:1)

Preparation 9

(S)-α-Benzyloxycarbonyl-γ-methylbutyl isocyanate (500 mg) and octahydroazocine (275 mg) were reacted in a similar manner to that of Preparation 7 to give N-(octahydroazocin-1-ylcarbonyl)-1-Leu-OBzl (680 mg).

mp : 87-89°C

Rf : 0.65 (n-hexane:EtOAc = 1:1)

Preparation 10

(2S)-2-Amino-3,3-dimethyl-N,N-dimethylbutyramide hydrochloride (0.25 g), (2S)-2-chlorocarbonyloxy-4-methylvaleric acid benzyl ester (0.36 g) and TEA (0.31 g) were reacted in ethyl acetate (10 ml) in a similar manner to that of Example 4-1) to give (2S)-2-[N-[(1S)-2,2-dimethyl-1-(N,N-dimethylcarbamoyl)propyl]carbamoyloxy]-4-methylvaleric acid benzyl ester (0.44 g).

Rf : 0.42 (hexane:EtOAc = 2:1)

Preparation 11

Benzyl (2R)-2-carboxymethyl-4-methylvalerate (1.35 g), hexahydro-1H-azepine (0.610 g) and WSCD·HCl (1.18 g) were reacted in methylene chloride (30 ml) in a similar manner to that of Preparation 1-1) to give benzyl (2R)-2-(hexahydro-1H-azepin-1-ylcarbonylmethyl)-4-methylvalerate (1.65 g).

Rf : 0.87 (benzene:EtOAc:AcOH = 20:20:1)

Preparation 12

The following compounds were obtained by catalytic reduction of the corresponding benzyl esters in a similar manner to that of Preparation 4-2).

1) N-[(1S)-2,2-Dimethyl-1-(N,N-dimethylcarbamoyl)propyl]carbamoyl]-1-Leu-OH.
mp : 90-93°C
Rf : 0.50 ($CHCl_3$:MeOH:AcOH = 16:1:1)

2) (2S)-2-[N-[(1S)-2,2-Dimethyl-1-(N,N-dimethylcarbamoyl)propyl]carbamoyloxy]-4-methylvaleric acid.
mp : 146-148°C
Rf : 0.20 ($CHCl_3$:MeOH = 9:1)

3) N-(Hexahydro-1H-azepin-1-ylcarbonyl)-1-Leu-OH. Rf : 0.40 (benzene:EtOAc:AcOH = 20:20:1)

4) (2R)-2-(Hexahydro-1H-azepin-1-ylcarbonylmethyl)-4-methylvaleric acid.
Rf : 0.55 (benzene:EtOAc:AcOH = 20:20:1)

5) N-(Octahydroazocin-1-ylcarbonyl)-1-Leu-OH.
Rf : 0.45 (benzene:EtOAc:AcOH = 20:20:1)

Preparation 13

The following compounds could be obtained by reacting the corresponding starting compounds with 2HCl·H-D-Pya-OC_2H_5 in the presence of NMM in a similar manner to that of Preparation 1-1).

1) Boc-D-Trp(i-C_4H_9)-D-Pya-OC_2H_5
mp : 60-62°C
Rf : 0.62 ($CHCl_3$: MeOH = 9:1)

2) Boc-D-Trp(CHO)-D-Pya-OC_2H_5
mp : 131-134°C
Rf : 0.60 ($CHCl_3$:MeOH = 9:1)

3) Boc-D-Trp(C_2H_5)-D-Pya-OC_2H_5
mp : 64-67°C
Rf : 0.61 ($CHCl_3$:MeOH = 9:1)

4) Boc-D-Trp(n-C_3H_7)-D-Pya-OC_2H_5
mp : 62-63°C
Rf : 0.60 ($CHCl_3$:MeOH = 9:1)

Preparation 14

The following compounds could be obtained by removing tert-butoxycarbonyl groups from the corresponding starting compounds with TFA and anisole in a similar manner to that of Preparation 1-2).

1) 2HCl·H-D-Trp(i-C_4H_9)-D-Pya-OC_2H_5
Rf : 0.09 ($CHCl_3$:MeOH = 9:1)

2) 2HCl·H-D-Trp(CHO)-D-Pya-OC_2H_5
Rf : 0.15 ($CHCl_3$:MeOH = 9:1)

3) HCl·H-D-Trp(C_2H_5)-D-Pya-OC_2H_5
Rf : 0.15 ($CHCl_3$:MeOH = 9:1)

4) HCl·H-D-Trp(n-C_3H_7)-D-Pya-OC_2H_5
Rf : 0.13 ($CHCl_3$:MeOH = 9:1)

Preparation 15

The following compounds could be obtained by reacting (S)-α-benzyloxycarbonyl-γ-methylbutyl isocyanate with the corresponding amines in a similar manner to that of Preparation 7.

1)) N-(Thiomorpholinocarbonyl)-1-Leu-OBzl
mp : 89-91°C
Rf : 0.53 (n-hexane:AcOEt = 1:1)

2) N-(1,2,3,4-Tetrahydroisoquinolin-2-ylcarbonyl)-L-Leu-OBzl
Rf : 0.71 (n-hexane:AcOEt = 1:1)

3) N-(1,2,3,4-Tetrahydroquinolin-1-ylcarbonyl)-L-Leu-OBzl
Rf : 0.62 (n-hexane:AcOEt = 2:1)

4) N-(N,N-Dibutylcarbamoyl)-1-Leu-OBzl
Rf : 0.70 (n-hexane:AcOEt = 2:1)

5) N-(N,N-Dipropylcarbamoyl)-1-Leu-OBzl
Rf : 0.69 (n-hexane:AcOEt = 2:1)

6) N-(N-Heptylcarbamoyl)-1-Leu-OBzl
Rf : 0.63 (n-hexane:AcOEt = 2:1)

7) N-(N,N-Diisobutylcarbamoyl)-1-Leu-OBzl
Rf : 0.76 (n-hexane:AcOEt = 2:1)

8) N-(N-Cyclohexyl-N-methylcarbamoyl)-1-Leu-OBzl
Rf : 0.82 (n-hexane:AcOEt = 1:1)

9) N-[4-(N,N-Dimethylcarbamoyl)piperidinocarbonyl]-L-Leu-OBzl
Rf : 0.53 ($CHCl_3$:MeOH:AcOH = 16:1:1)

10) N-(2-Pyridylcarbamoyl)-1-Leu-OBzl
Rf : 0.61 ($CHCl_3$:MeOH = 9:1)

11) N-[(2S)-2-(N,N-Dimethylcarbamoyl)pyrrolidin-1-ylcarbonyl)-1-Leu-OBzl
Rf : 0.47 ($CHCl_3$:MeOH = 9:1)

12) N-[(2R)-2-(N,N-Dimethylcarbamoyl)pyrrolidin-1-ylcarbonyl)-1-Leu-OBzl
Rf : 0.51 ($CHCl_3$:MeOH = 9:1)

13) N-[1-(N,N-Dimethylcarbamoyl)cyclohexylcarbamoyl]-L-Leu-OBzl
mp : 145-148°C
Rf : 0.61 ($CHCl_3$:MeOH = 9:1)

14) N-[(1S,2S)-1-(N,N-Diethylcarbamoyl)-2-methylbutylcarbamoyl]-1-Leu-OBzl
Rf : 0.31 (n-hexane:AcOEt = 2:1)

15) N-(1,2,3,6-Tetrahydropyridin-1-ylcarbonyl)-1-Leu-OBzl
Rf : 0.49 (n-hexane:AcOEt = 2:1)

16) N-(2,6-Dimethylpiperidinocarbonyl)-1-Leu-OBzl
mp : 81-83°C
Rf : 0.53 (n-hexane:AcOEt = 2:1)

17) N-(3,5-Dimethylpiperidinocarbonyl)-1-Leu-OBzl
Rf : 0.60 (n-hexane:AcOEt = 2:1)

18) N-(N,N-Dicyclohexylcarbamoyl)-1-Leu-OBzl
mp : 100-103°C
Rf : 0.80 (n-hexane:AcOEt = 2:1)

19) N-(N,N-Diethylcarbamoyl)-1-Leu-OBzl
Rf : 0.45 (n-hexane:AcOEt = 2:1)

20) N-(N,N-Diisopropylcarbamoyl)-1-Leu-OBzl
Rf : 0.65 (n-hexane:AcOEt = 2:1)

21) N-[N-Methyl-N-[(1S)-3-methyl-1-(N,N-dimethylcarbamoyl)butyl]carbamoyl]-1-Leu-OBzl
mp : 183-187°C
Rf : 0.38 ($CHCl_3$:MeOH:AcOH = 16:1:1)

22) N-[(1S)-1-(N,N-Dimethylcarbamoyl)pentylcarbamoyl]-L-Leu-OBzl
mp : 133-136°C
Rf : 0.59 (n-hexane:AcOEt = 2:1)

23) N-[N-Methyl-N-[(1S,2S)-1-(N,N-dimethylcarbamoyl)-2-methylbutyl]carbamoyl]-1-Leu-OBzl
Rf : 0.60 (n-hexane:AcOEt = 2:1)

24) N-[(1S)-1-(N,N-Dimethylcarbamoyl)ethylcarbamoyl)]-L-Leu-OBzl
Rf : 0.55 (n-hexane:AcOEt = 2:1)

Preparation 16

To a solution of benzyl (2S)-2-chlorocarbonyloxy-4-methylvalerate (0.56 g) in tetrahydrofuran (11 ml) was added cyclohexylamine (0.40 g) at room temperature. After being stirred for 10 minutes, the solvent was removed by evaporation under reduced pressure, and the residue was dissolved in ethyl acetate (30 ml). The solution was washed with 1N HCl, water and brine successively. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residual solid was triturated with hexane to give benzyl (2S)-2-cyclohexylcarbamoyloxy-4-methylvalerate (0.45 g).
mp : 89-90°C
Rf : 0.70 (n-hexane:AcOEt = 2:1)

Preparation 17

The following compounds could be obtained by reacting benzyl (2S)-2-chlorocarbonyloxy-4-methylvalerate with the corresponding amines in a similar manner to that of Preparation 16.

1) Benzyl (2S)-4-methyl-2-[(2S)-2-methylbutylcarbamoyloxy]valerate
mp : 48-49°C
Rf : 0.69 (n-hexane:AcOEt = 2:1)

2) Benzyl (2S)-4-methyl-2-[(1S,2S)-2-methyl-1-(N,N-dimethylcarbamoyl)butylcarbamoyloxy]valerate
Rf : 0.91 ($CHCl_3$:MeOH = 9:1)

3) Benzyl (2S)-4-methyl-2-[(1R,2S)-2-methyl-1-(N,N-dimethylcarbamoyl)butylcarbamoyloxy]valerate
Rf : 0.36 (n-hexane:AcOEt = 2:1)

4) Benzyl (2S)-4-methyl-2-[(1S)-2-methyl-1-(N,N-dimethylcarbamoyl)propylcarbamoyloxy]valerate
Rf : 0.36 (n-hexane:AcOEt = 2:1)

5) Benzyl (2S)-4-methyl-2-[(1S)-3-methyl-1-(N,N-dimethylcarbamoyl)butylcarbamoyloxy]valerate
Rf : 0.37 (n-hexane:AcOEt = 2:1)

6) Benzyl (2S)-4-methyl-2-[(1S,2S)-2-methyl-1-(piperidinocarbonyl)butylcarbamoyloxy]valerate
Rf : 0.36 (n-hexane:AcOEt = 2:1)

7) Benzyl (2S)-4-methyl-2-[(1S,2S)-1-carbamoyl-2-methylbutylcarbamoyloxy]valerate
mp : 140-141°C
Rf : 0.13 (n-hexane:AcOEt = 2:1)

8) Benzyl (2S)-2-[(1S,2S)-1-(isopropylcarbamoyl)-2-methylbutylcarbamoyloxy]-4-methylvalerate
mp : 90-92°C
Rf : 0.67 (n-hexane:AcOEt = 2:1)

9) Benzyl (2S)-4-methyl-2-(piperidinocarbonyloxy)-valerate
Rf : 0.70 (n-hexane:AcOEt = 2:1)

10) Benzyl (2S)-2-[(1S,2S)-1-(cyclohexylcarbamoyl)-2-methylbutylcarbamoyloxy]-4-methylvalerate
mp : 98-100°C
Rf : 0.55 (n-hexane:AcOEt = 2:1)

11) Benzyl (2S)-2-(hexahydro-1H-azepin-1-ylcarbonyloxy)-4-methylvalerate
Rf : 0.78 (n-hexane:AcOEt = 2:1)

12) Benzyl (2S)-2-(1,2,3,4-tetrahydroisoquinolin-2-ylcarbonyloxy)-4-methylvalerate
Rf : 0.68 (n-hexane:AcOEt = 2:1)

Preparation 18

To a solution of benzyl (2R)-2-carboxymethyl-4-methylvalerate (527 mg) and cyclohexylamine (238 mg) in methylene chloride (10 ml) was added WSCD·HCl (460 mg) at room temperature. After being stirred overnight, the mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (30 ml). The solution was washed with 5% HCl, water, saturated sodium bicarbonate and water, dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with n-hexane to give benzyl (2R)-2-(cyclohexylcarbamoylmethyl)-4-methylvalerate (410 mg).
mp : 99-102°C
Rf : 0.84 (benzene:AcOEt:AcOH = 20:20:1)

Preparation 19

Benzyl (2R)-2-carboxymethyl-4-methylvalerate (320 mg), octahydroazocin (165 mg) and WSCD·HCl (280 mg) were reacted in methylene chloride (20 ml) in a similar manner to that of Preparation 18 to give benzyl (2R)-2-(octahydroazocin-1-ylcarbonylmethyl)-4-methylvalerate (378 mg).
Rf : 0.83 (benzene:AcOEt:AcOH = 20:20:1)

Preparation 20

The following compounds could be obtained by reducing the corresponding benzyl ester compounds in the presence of 10% palladium on carbon in a similar manner to that of Preparation 1-4).

1) N-(1,2,3,4-Tetrahydroisoquinolin-2-ylcarbonyl)-L-Leu-OH
mp : 93-95°C
Rf : 0.32 (benzene:AcOEt:AcOH = 20:20:1)

2) N-(1,2,3,4-Tetrahydroquinolin-1-ylcarbonyl)-L-Leu-OH
Rf : 0.46 (benzene:AcOEt:AcOH = 20:20:1)

3) N-(N,N-Dibutylcarbamoyl) -1-Leu-OH
mp : 121-123°C
Rf : 0.51 (benzene:AcOEt:AcOH = 20:20:1)

4) N-(N,N-Dipropylcarbamoyl)-1-Leu-OH
Rf : 0.41 (benzene:AcOEt:AcOH = 20:20:1)

5) N-(N-Heptylcarbamoyl)-1-Leu-OH

Rf : 0.48 (benzene:AcOEt:AcOH = 20:20:1)

6) N-(N,N-Diisobutylcarbamoyl)-1-Leu-OH
mp : 116-118°C
Rf : 0.39 (benzene:AcOEt:AcOH = 20:20:1)

7) N-(N-Cyclohexyl-N-methylcarbamoyl)-1-Leu-OH
Rf : 0.51 (benzene:AcOEt:AcOH = 20:20:1)

8) N-[4-(N,N-Dimethylcarbamoyl)piperidinocarbonyl]-L-Leu-OH
Rf : 0.10 ($CHCl_3$:MeOH:AcOH = 16:1:1)

9) N-(2-Pyridylcarbamoyl)-1-Leu-OH
Rf : 0.19 ($CHCl_3$:MeOH:AcOH = 16:1:1)

10) N-[(2S)-2-(N,N-Dimethylcarbamoyl)pyrrolidin-1-ylcarbonyl)-1-Leu-OH
Rf : 0.34 ($CHCl_3$:MeOH:AcOH = 16:1:1)

11) N-[(2R)-2-(N,N-Dimethylcarbamoyl)pyrrolidin-1-ylcarbonyl)-1-Leu-OH
Rf : 0.34 ($CHCl_3$:MeOH:AcOH = 16:1:1)

12) N-[1-(N,N-Dimethylcarbamoyl)cyclohexylcarbamoyl]-L-Leu-OH
mp : 191-192°C
Rf : 0.35 ($CHCl_3$:MeOH:AcOH = 16:1:1)

13) N-[(1S,2S)-1-(N,N-Dimethylcarbamoyl)-2-methylbutylcarbamoyl]-1-Leu-OH
Rf : 0.35 ($CHCl_3$:MeOH:AcOH = 16:1:1)

14) N-(2,6-Dimethylpiperidinocarbonyl)-1-Leu-OH
Rf : 0.53 ($CHCl_3$:MeOH:AcOH = 16:1:1)

15) N-(3,5-Dimethylpiperidinocarbonyl)-1-Leu-OH
Rf : 0.53 ($CHCl_3$:MeOH:AcOH = 16:1:1)

16) N-(N,N-Dicyclohexylcarbamoyl)-1-Leu-OH
mp : 62-73°C
Rf : 0.42 ($CHCl_3$:MeOH:AcOH = 16:1:1)

17) N-(N,N-Diethylcarbamoyl)-1-Leu-OH
mp : 106-107°C
Rf : 0.36 ($CHCl_3$:MeOH:AcOH = 16:1:1)

18) N-(N,N-Diisopropylcarbamoyl)-1-Leu-OH
Rf : 0.38 ($CHCl_3$:MeOH:AcOH = 16:1:1)

19) N-[N-Methyl-N-[(1S)-3-methyl-1-(N,N-dimethylcarbamoyl)butyl]carbamoyl]-1-Leu-OH
Rf : 0.38 ($CHCl_3$:MeOH:AcOH = 16:1:1)

20) N-[(1S)-1-(N,N-Dimethylcarbamoyl)pentylcarbamoyl]-L-Leu-OH
mp : 155-160°C
Rf : 0.34 ($CHCl_3$:MeOH:AcOH = 16:1:1)

21) N-[N-Methyl-N-[(1S,2S)-1-(N,N-Dimethylcarbamoyl)-2-methylbutyl]carbamoyl]-1-Leu-OH
Rf : 0.52 ($CHCl_3$:MeOH:AcOH = 16:1:1)

22) N-[(1S)-1-(N,N-Dimethylcarbamoyl)ethylcarbamoyl)]-L-Leu-OH
Rf : 0.46 ($CHCl_3$:MeOH:AcOH = 16:1:1)

23) (2S)-2-Cyclohexylcarbamoyloxy-4-methylvaleric acid
Rf : 0.45 ($CHCl_3$:MeOH = 9:1)

24) (2S)-4-Methyl-2-[(2S)-2-methylbutylcarbamoyloxy]-valeric acid
Rf : 0.40 ($CHCl_3$:MeOH = 9:1)

25) (2S)-4-Methyl-2-[(1S,2S)-2-methyl-1-(N,N-dimethylcarbamoyl)butylcarbamoyloxy]valeric acid
Rf : 0.50 ($CHCl_3$:MeOH:AcOH = 16:1:1)

26) (2S)-4-Methyl-2-[(1R,2S)-2-methyl-1-(N,N-dimethylcarbamoyl)butylcarbamoyloxy]valeric acid
Rf : 0.33 ($CHCl_3$:MeOH:AcOH = 16:1:1)

27) (2S)-4-Methyl-2-[(1S)-2-methyl-1-(N,N-Dimethylcarbamoyl)propylcarbamoyloxy]valeric acid
Rf : 0.31 ($CHCl_3$:MeOH:AcOH = 16:1:1)

28) (2S)-4-Methyl-2-[(1S)-3-methyl-1-(N,N-dimethylcarbamoyl)butylcarbamoyloxy]valeric acid
Rf : 0.35 ($CHCl_3$:MeOH:AcOH = 16:1:1)

29) (2S)-4-Methyl-2-[(1S,2S)-1-carbamoyl-2-methylbutylcarbamoyloxy]valeric acid
mp : 170-175°C
Rf : 0.50 ($CHCl_3$:MeOH:AcOH = 16:1:1)

30) (2S)-2-[(1S,2S)-1-(Isopropylcarbamoyl)-2-methylbutylcarbamoyloxy]-4-methylvaleric acid
mp : 179-180°C
Rf : 0.37 ($CHCl_3$:MeOH:AcOH = 16:1:1)

31) (2S)-4-Methyl-2-(Piperidinocarbonyloxy)valeric acid
Rf : 0.56 ($CHCl_3$:MeOH:AcOH = 16:1:1)

32) (2S)-2-[(1S,2S)-1-(Cyclohexylcarbamoyl)-2-methylbutylcarbamoyloxy]-4-methylvaleric acid
mp : 193-195°C
Rf : 0.43 ($CHCl_3$:MeOH:AcOH = 16:1:1)

33) (2S)-2-(Hexahydro-1H-azepin-1-ylcarbonyloxy)-4-methylvaleric acid
mp : 86-88°C
Rf : 0.53 (benzene:AcOEt:AcOH = 20:20:1)

34) (2S)-2-(1,2,3,4-Tetrahydroisoquinolin-2-ylcarbonyloxy-4-methylvaleric acid
Rf : 0.48 (benzene:AcOEt:AcOH = 20:20:1)

35) (2R)-2-(Cyclohexylcarbamoylmethyl)-4-methylvaleric acid
mp : 86-88°C
Rf : 0.53 (benzene:AcOEt:AcOH = 20:20:1)

36) (2R)-2-(Octahydroazocin-1-ylcarbonylmethyl)-4-methylvaleric acid
mp : 79-81°C
Rf : 0.56 (benzene:AcOEt:AcOH = 20:20:1)

37) N-Cyclohexylcarbamoyl-1-Leu-OH
mp : 105-108°C
Rf : 0.32 ($CHCl_3$:MeOH = 9:1)

38) N-[1-(N,N-Dimethylcarbamoylmethyl)cyclohexylcarbamoyl]-1-Leu-OH
Rf : 0.35 ($CHCl_3$:MeOH:AcOH = 16:1:1)

39) N-Cyclohexylcarbamoyl-1-Leu-D-Trp(CH_3)-OH
mp : 202-206°C
Rf : 0.51 ($CHCl_3$:MeOH:AcOH = 8:1:1)

40) N-(Piperidinocarbamoyl)-1-Leu-OH
mp : 185-187°C
Rf : 0.70 ($CHCl_3$:MeOH = 9:1)

41) N-[(2S)-2-Methylbutylcarbamoyl]-1-Leu-OH
Rf : 0.22 ($CHCl_3$:MeOH:AcOH = 8:1:1)

42) N-(2-Pyridylmethylcarbamoyl)-1-Leu-OH
mp : 183-185°C
Rf : 0.23 ($CHCl_3$:MeOH:AcOH = 8:1:1)

43) N-[(1S,2S)-1-(N,N-Dimethylcarbamoyl)-2-methylbutylcarbamoyl]-1-Leu-OH
mp : 185-187°C
Rf : 0.27 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Preparation 21

To a solution of N-(1,2,3,6-tetrahydropyridin-1-ylcarbonyl)-1-Leu-OBzl (0.58 g) in MeOH (6 ml) was added 1N NaOH (3.5 ml) at room temperature. After one hour, the mixture was acidified with 1N HCl (5 ml) and the solvent was removed by evaporation in vacuo. The residue was dissolved in ethyl acetate (20 ml) and washed with water (20 ml) and brine (20 ml). The organic layer was dried over magnesium sulfate and concentrated in vacuo to give N-(1,2,3,6-tetrahydropyridin-1-ylcarbonyl)-1-Leu-OH (0.31 g) as an oil.
Rf : 0.42 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Preparation 22

The following compounds could be obtained by hydrolyzing the corresponding benzyl ester compounds with 1N NaOH in a similar manner to that of Preparation 21.

1) N-(Thiomorpholinocarbonyl)-1-Leu-OH
Rf : 0.31 (benzene:AcOEt:AcOH = 20:20:1)

2) (2S)-2-[(1S,2S)-1-(Piperidinocarbonyl)-2-methylbutylcarbamoyloxy]-4-methylvaleric acid
Rf : 0.47 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Preparation 23

L-Leu-OH (10.0 g) was dissolved in water (150 ml) containing concentrated sulfuric acid (3.2 ml) at 0°C. To the solution was added dropwise a solution of sodium nitrate (7.9 g) in water (50 ml) over 1 hour. The mixture was saturated with sodium chloride and extracted with ethyl acetate (500 ml). The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residual solid was triturated with hexane to give (2S)-2-hydroxy-4-methylvaleric acid (6.51 g).
mp : 70-72°C
Rf : 0.80 (n-BuOH:AcOH:H_2O = 4:1:1)

Preparation 24

To a stirring solution of (2S)-2-hydroxy-4-methylvaleric acid (5.0 g) and benzyl bromide (4.95 ml) in DMF (50 ml) was added potassium carbonate (3.13 g) at room temperature. After being stirred for 12 hours, the solvent was removed by evaporation in vacuo. The residue was dissolved in ethyl acetate (100 ml) and washed with water, 1N HCl and brine successively. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residual oil was purified with silica gel column chromatography (hexane-ethyl acetate as an eluent) to give benzyl (2S)-2-hydroxy-4-methylvalerate (8.2 g) as a colorless oil.
Rf : 0.67 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Preparation 25

To a solution of benzyl (2S)-2-hydroxy-4-methylvalerate (1.00 g) in tetrahydrofuran (20 ml) was added trichlorome-

thyl chloroformate (0.55 ml) at room temperature. The solution was refluxed for 11 hours and the solvent was removed by evaporation at atmospheric pressure to give benzyl (2S)-2-chlorocarbonyloxy-4-methylvalerate (1.26 g) as an oil.
Rf : 0.81 (n-hexane:AcOEt = 2:1)

Preparation 26

A solution of benzyl (2R)-2-t-butoxycarbonylmethyl-4-methylvalerate (3.40 g) in TFA (60 ml) was stirred for 1 hour under ice-bath cooling. Evaporation of TFA gave benzyl (2R)-2-carboxymethyl-4-methylvalerate (2.72 g) as an oil.
Rf : 0.73 (benzene:AcOEt:AcOH = 20:20:1)

Preparation 27

The following compounds could be obtained by reacting the corresponding starting compounds with phenyl isocyanate in Et_3N or NMM in a similar manner to that of Preparation 7.

1) N-Cyclohexylcarbamoyl-1-Leu-OBzl
mp : 120-125°C
Rf : 0.73 ($CHCl_3$:MeOH = 9:1)

2) N-Cyclohexylcarbamoyl-1-Leu-D-Trp(CH_3)-OBzl
mp : 190-193°C
Rf : 0.74 ($CHCl_3$:MeOH = 9:1)

Preparation 28

The following compounds could be obtained by reacting TsOH·H-1-Leu-OBzl with the corresponding amines in the presence of trichloromethyl chloroformate in a similar manner to that of Example 72.

1) N-[1-(N,N-Dimethylaminocarbonylmethyl)-cyclohexylcarbamoyl]-1-Leu-OBzl
Rf : 0.70 ($CHCl_3$:MeOH = 9:1)

2) N-[(1S,2S)-1-(N,N-Dimethylcarbamoyl-2-methylbutylcarbamoyl)-1-Leu-OBzl
mp : 95-98°C
Rf : 0.32 (n-hexane:AcOEt = 1:1)

3) N-(Piperidinocarbamoyl)-1-Leu-OBzl
Rf : 0.43 (n-hexane:AcOEt = 1:1)

4) N-(2-Pyridylmethylcarbamoyl)-1-Leu-OBzl
Rf : 0.50 (AcOEt)

5) N-[(2S)-2-Methylbutylcarbamoyl]-1-Leu-OBzl
mp : 73-75°C
Rf : 0.29 (n-hexane:AcOEt = 3:1)

Preparation 29

1) A mixture of TSOH·H-1-Leu-OBzl (12.0 g), ethyl acetate (150 ml) and 1M sodium bicarbonate (150 ml) was stirred at room temperature for 20 minutes. The separated organic phase was washed with 1M sodium bicarbonate and a saturated aqueous sodium chloride, and then dried over magnesium sulfate. To this solution was added 4N hydrogen chloride in ethyl acetate (15.3 ml), followed by stirring for 5 minutes under ice-cooling. Removal of the solvent gave HCl·H-1-Leu-OBzl (7.66 g).

2) To a solution of the above product (7.6 g) in toluene (228 ml) were added charcoal (380 mg) and a solution of trichloromethyl chloroformate (3.6 ml) in toluene (7.6 ml), and the mixture was stirred at 120°C for 2 hours and then filtered. The solvent was removed from the filtrate and the residue was dissolved in toluene (152 ml). This solution was evaporated to give (S)-α-benzyloxycarbonyl-γ-methylbutylisocyanate (7.58 g).

3) To a solution of this product in ethyl acetate (114 ml) was added hexahydro-1H-azepin (3.5 g) under ice-cooling, and the mixture was stirred at the same temperature for 30 minutes. The resultant solution was washed with 5% HCl, aqueous sodium bicarbonate and saturated aqueous sodium chloride and then dried over magnesium sulfate. Removal of the solvent gave N-(hexahydro-1H-azepin-1-ylcarbonyl)-1-Leu-OBzl (9.96 g).

Rf : 0.71 (n-hexane:EtOAc = 2:1)

4) To a solution of N-(hexahydro-1H-azepin-1-ylcarbonyl)-1-Leu-OBzl (9.0 g) in ethanol (69 ml) was catalytically reduced with 10% palladium on carbon (0.692 g) under 3 atmospheric pressure of hydrogen for 30 minutes. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in ethyl acetate (138 ml), and this solution was washed with 5% HCl and saturated aqueous sodium chloride and then dried. Removal of the solvent gave a residue, which was crystallized from ethyl acetate and hexane to afford N-(hexahydro-1H-azepin-1-ylcarbonyl)-1-Leu-OH (5.7 g).

mp : 90-92°C

Rf : 0.43 (benzene:EtOAc:AcOH = 20:20:1)

Preparation 30

1) To a solution of Boc-D-Trp-OH (15.0 g) in DMF (150 ml) were added potassium tert-butoxide (13.8 g) and methyl iodide (10.5 g) under ice-cooling. After stirring under ice-cooling for 30 minutes and at room temperature for 15 minutes, the reaction mixture was poured into ice-cooled 0.24 N HCl, followed by extraction with ethyl acetate. The extract was washed with 5% $NaHSO_3$ and saturated aqueous sodium chloride. Removal of the solvent gave a residue, which was crystallized from diisopropyl ether to afford Boc-D-Trp(CH_3)-OH (9.18 g).

Rf : 0.61 ($CHCl_3$:MeOH = 8:2)

2) To a solution of this product (6.84 g) in dichloromethane (137 ml) were added NMM (2.17 g) and isobutyl chloroformate (2.93 g) at -30°C. Thereto was added 2HCl·H-D-Pya-OC_2H_5 (6.0 g) at -15 to -10°C and then NMM (4.54 g) at -20°C, and the mixture was stirred at the same temperature for 30 minutes. The reaction mixture was washed with 1M sodium bicarbonate and saturated aqueous sodium chloride, and then treated with charcoal. The solvent was removed by evaporation and the residue was crystallized from ethyl acetate and hexane to give Boc-D-Trp(CH_3)-D-Pya-OC_2H_5 (7.88 g).

mp : 99-101°C

Rf : 0.80 ($CHCl_3$:MeOH = 9:1)

$[\alpha]_D^{23}$: +26.5° (C=1.0, MeOH)

3) To a solution of the above product (7.8 g) in ethyl acetate (61.7 ml) was added 4N hydrogen chloride in ethyl acetate (30.8 ml) under ice-cooling, and this mixture was stirred at room temperature for an hour. The desired product was collected by decantation and triturated with ethyl acetate to give 2HCl·H-D-Trp(CH3)-D-Pya-OC_2H_5 (7.4 g).

Preparation 31-1)

N^{α}-Boc-N^{α}-methyl-N^{in}-methyl-D-Trp-OH (0.65 g), 2HCl·H-D-Pya-OEt (0.52 g) HOBt (0.32 g), WSCD (0.36 g), Et_3N (0.20 g) and DMF (20 ml) were reacted in a similar manner to that of Preparation 1-1) to give N^{α}-Boc-N^{α}-methyl-N^{in}-methyl-D-Trp-D-Pya-OEt (0.78 g).

Rf = 0.81 ($CHCl_3$:MeOH = 9:1)

Preparation 31-2)

Boc-D-Trp(CHO)-OH (2.0 g), 2HCl·H-D-Pya-OEt (1.61 g), WSCD (1.03 g), HOBt (0.90 g), NMM (0.61 g) and DMF (20 ml) were reacted in a similar manner to that of Preparation 1-1) to give Boc-D-Trp(CHO)-D-Pya-OEt (2.23 g).

mp : 136-137°C

Rf : 0.65 (ethyl acetate)

Preparation 31-3)

To a solution of Boc-D-Trp(CHO)-OH (0.79 g) and N-methylmorpholine (0.13 ml) in methylene chloride (20 ml) was added dropwise isobutyl chloroformate (0.31 ml) at -15°C. After 15 minutes, N-methylmorpholine (0.13 ml) and HCl·H-D-Glu(OBzl)-OPac (0.85 g) were added to this solution at -30°C. After being stirred for 1 hour, the mixture was

washed with 0.5N hydrochloric acid (10 ml), water (10 ml) and 1M sodium hydrogen carbonate (10 ml), dried over magnesium sulfate and concentrated in vacuo. The residual solid was triturated with ethyl ether to give Boc-D-Trp (CHO)-D-Glu(OBzl)-OPac (1.31 g).

mp : 142-144°C

Rf : 0.79 (chloroform:methanol = 9:1)

Preparation 31-4)

Boc-D-Trp(CHO)-D-Phe-OPac was obtained in a similar manner to that of Preparation 1-1).

mp : 142-146°C

Rf : 0.78 (chloroform:methanol = 9:1)

Preparation 31-5)

Boc-D-Trp(CHO)-OH (1.0 g), HCl·H-βAla-OPac (0.81 g), HOBT (0.49 g), WSCD (0.56 g) and DMF (10 ml) were reacted in a similar manner to that of Preparation 1-1) to give Boc-D-Trp(CHO)-βAla-OPac (3.15 g).

mp : 153-155°C

Rf : 0.58 (chloroform:methanol = 9:1)

Preparation 31-6)

Boc-D-Trp(CHO)-OH (10.0 g), HCl·H-βAla-OMe (4.41 g) HOBt (4.47 g), WSCD (5.14 g) and DMF (100 ml) were reacted in a similar manner to that of Preparation 1-1) to give Boc-D-Trp(CHO)-βAla-OMe (8.77 g).

mp : 134-135°C

Rf : 0.54 ($CHCl_3$:MeOH = 9:1)

Preparation 31-7)

Boc-D-Phe-OH (265 mg), 2HCl·H-D-Pya-OEt (267 mg), HOBt (0.16 g) WSCD (0.19 g), N-methylmorpholine (0.10 g) and DMF (6 ml) were reacted in a similar manner to that of Preparation 1-1) to give Boc-D-Phe-D-Pya-OEt (0.32 g).

mp : 97-99°C

Rf : 0.58 ($CHCl_3$:MeOH = 9:1)

The following compounds could be obtained by removing t-butoxycarbonyl groups from the corresponding starting compounds in a similar manner to that of Preparation 1-2).

Preparation 32-1)

HCl·H-D-Trp(Me)-D-Leu-OBzl

mp : 85-90°C

Rf : 0.27 ($CHCl_3$:MeOH = 9:1)

Preparation 32-2)

2HCl·N^{α}-methyl-D-Trp(Me)-D-Pya-OEt

mp : 100-110°C

Rf : 0.50 ($CHCl_3$:MeOH = 9:1)

Preparation 32-3)

2HCl·H-D-Trp(CHO)-D-Pya-OEt

Rf : 0.16 ($CHCl_3$:MeOH:AcOH = 8:1:1, V/V)

Preparation 32-4)

HCl·H-D-Trp(CHO)-D-Glu(OBzl)-OPac

mp : 80-89°C

Rf = 0.50 (chloroform:methanol = 9:1)

Preparation 32-5)

HCl·H-D-Trp(CHO)-D-Phe-OPac
mp : 185°C (dec.)
Rf : 0.37 (chloroform:methanol:acetic acid = 16:1:1)

Preparation 32-6)

HCl·H-D-Trp(CHO)-βAla-OPac
mp : 157-164°C
Rf : 0.17 (chloroform:methanol:acetic acid = 16:1:1)

Preparation 32-7)

HCl·H-D-Trp(CHO)-βAla-OMe
mp : 168-169°C
Rf : 0.53 (10% MeOH in $CHCl_3$)

Preparation 32-8)

2HCl·H-D-Phe-D-Pya-OEt
Rf : 0.12 (10% MeOH in $CHCl_3$)

The following compounds could be obtained by reacting (S)-α-benzyloxycarbonyl-γ-methylbutyl isocyanate with the corresponding amines in a similar manner to that of Preparation 7.

Preparation 33-1)

N-(Pyrrolidin-1-ylcarbonyl)-1-Leu-OBzl
Rf : 0.14 (EtOAc:hexane = 1:2)

Preparation 33-2)

N-(Piperidin-1-ylcarbonyl)-1-Leu-OBzl
mp : 75-76°C
Rf : 0.27 (EtOAc:hexane = 1:2)

Preparation 33-3)

N-[(2S)-4-Methyl-2-(1-methylpropyl)-3-oxopiperidin-1-ylcarbonyl]-1-Leu-OBzl
Rf : 0.13 (EtOAc:hexane = 1:1, V/V)

Preparation 33-4)

N-[{(1S)-1-(N,N-Dimethylcarbamoyl)-1-cyclohexylmethyl}carbamoyl]-1-Leu-OBzl
Rf : 0.26 (EtOAc:hexane = 1:1, V/V)

Preparation 33-5)

N-[{(1S)-1-(N,N-Dimethylcarbamoyl)-1-phenylmethyl}-carbamoyl]-1-Leu-OBzl
Rf : 0.08 (EtOAc:hexane = 1:2, V/V)

Preparation 33-6)

N-[{cis-4-(N,N-Dimethylcarbamoylmethyl)cyclohexyl}-carbamoyl]-1-Leu-OBzl
Rf : 0.25 (ethyl acetate)

Preparation 33-7)

N-[{cis-4-(N,N-Dimethylcarbamoyl)cyclohexyl}-carbamoyl]-1-Leu-OBzl
Rf : 0.34 (ethyl acetate)

Preparation 33-8)

N-(N,N-Dimethylcarbamoylmethyl)carbamoyl-1-Leu-OBzl
Rf : 0.23 (ethyl acetate)

Preparation 33-9)

N-[{2-(N,N-Dimethylcarbamoyl)ethyl}carbamoyl]-L-Leu-OBzl
Rf : 0.33 (ethyl acetate)

Preparation 33-10)

N-[(trans-4-Hydroxycyclohexyl)carbamoyl]-1-Leu-OBzl
mp : 169-171°C
Rf : 0.53 (ethyl acetate)

Preparation 33-11)

N-[{(1S)-1-(Hydroxymethyl)-3-methylbutyl}carbamoyl]-L-Leu-OBzl
Rf : 0.38 (n-hexane:ethyl acetate = 1:1)

Preparation 33-12

N-[{2-(Morpholino)ethyl}carbamoyl]-1-Leu-OBzl
Rf : 0.46 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Preparation 33-13)

N-(ε-Caprolactam-3-ylcarbamoyl)-1-Leu-OBzl
mp : 148-150°C
Rf = 0.52 (ethyl acetate)

Preparation 33-14)

N-(N'-Isobutyrylhydrazinocarbonyl)-1-Leu-OBzl
mp : 93-96°C
Rf : 0.16 (n-hexane:ethyl acetate = 1:1)

Preparation 33-15)

N-[(1-Ethoxycarbonylpiperidin-4-yl)carbamoyl]-L-Leu-OBzl
Rf : 0.35 (n-hexane:ethyl acetate = 1:1)

The following compounds were obtained by removing benzyl groups from the corresponding starting compounds in a similar manner to that of Preparation 1-4).

Preparation 34-1)

N-(Pyrrolidin-1-ylcarbonyl)-1-Leu-OH
Rf : 0.18 (10% MeOH in $CHCl_3$)

Preparation 34-2)

N-(Piperidinocarbonyl)-1-Leu-OH

Rf : 0.17 (10% MeOH in $CHCl_3$)

Preparation 34-3)

N-(2-Chlorophenylcarbamoyl)-1-Leu-OH
Rf : 0.20 (10% MeOH in $CHCl_3$)

Preparation 34-4)

N-(o-Chlorophenylacetyl)-1-Leu-OH
mp : 145-146°C
Rf : 0.21 (10% MeOH in $CHCl_3$)

Preparation 34-5)

(2R)-2-[{(1S)-1-(N,N-Dimethylcarbamoyl)-2,2-dimethylpropyl}carbamoyl]methyl-4-methylvaleric acid
Rf : 0.43 (10% MeOH in $CHCl_3$)

Preparation 34-6)

N-[(2S)-4-Methyl-2-(1-methylpropyl)-3-oxopiperazin-1-ylcarbonyl]-1-Leu-OH
mp : 180°C (dec.)
Rf : 0.20 (10% MeOH in $CHCl_3$)

Preparation 34-7)

N-[{(1S)-1-(N,N-Dimethylcarbamoyl)-1-cyclohexylmethyl}carbamoyl]-1-Leu-OH
mp : 210-211°C
Rf : 0.20 (10% MeOH in $CHCl_3$)

Preparation 34-8)

N-[{(1S)-1-(N,N-Dimethylcarbamoyl)-1-phenylmnthyl}carbamoyl]-1-Leu-OH
Rf : 0.38 ($CHCl_3$:MeOH:AcOH = 16:1:1, V/V)

Preparation 34-9)

N-(Hexahydro-1H-azepin-1-ylcarbonyl)-N-methyl-Leu-OH
Rf : 0.58 (benzene:ethyl acetate:acetic acid = 20:20:1, V/V)

Preparation 34-10)

N-[{cis-4-(N,N-Dimethylcarbamoylmethyl)cyclohexyl}-carbamoyl]-1-Leu-OH
Rf : 0.57 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Preparation 34-11)

N-[{cis-4-(N,N-Dimethylcarbamoyl)cyclohexyl}carbamoyl]-1-Leu-OH
Rf : 0.52 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Preparation 34-12)

N-(N,N-Dimethylcarbamoylmethyl)carbamoyl-1-Leu-OH
Rf : 0.73 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Preparation 34-13)

N-[{2-(N,N-Dimethylcarbamoyl)ethyl}carbamoyl]-L-Leu-OH

Rf : 0.77 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Preparation 34-14)

N-[(trans-4-Hydroxycyclohexyl)carbamoyl]-1-Leu-OH
Rf : 0.78 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Preparation 34-15)

N-[N-(2-Hydroxyethyl)-N-methylcarbamoyl]-1-Leu-OH
Rf : 0.65 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Preparation 34-16)

N-[{(1S)-(1-Hydroxymethyl)-3-methylbutyl}carbamoyl]-L-Leu-OH
Rf : 0.38 (benzene:ethyl acetate:acetic acid = 20:20:1)

Preparation 34-17)

N-[{2-(Morpholino)ethyl}carbamoyl]-1-Leu-OH
Rf : 0.21 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Preparation 34-18)

N-(ε-Caprolactam-3-ylcarbamoyl)-1-Leu-OH
Rf : 0.67 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Preparation 34-19)

N-(N'-Isobutyrylhydrazinocarbonyl)-1-Leu-OH
Rf : 0.45 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Preparation 34-20)

N-[(1-ethoxycarbonylpiperidin-4-yl)-carbamoyl]-L-Leu-OH
Rf : 0.48 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Preparation 35

Hexahydro-1H-azepine (0.3 g), (S)-α-benzyloxycarbonyl-γ,γ-dimethylbutylisocyanate (0.48 g) and EtOAc (10 ml) were reacted in a similar manner to that of Preparation 7 to give N-(hexahydro-1H-azepin-1-ylcarbonyl)-γ-methyl-1-Leu-OBzl. This product, 10% Pd-C (60 mg), MeOH (10 ml) and H_2O (1 ml) were reacted in a similar manner to that of Preparation 1-4) to give N-(hexahydro-1H-azepin-1-ylcarbonyl)-γ-methyl-1-Leu-OH (0.43 g).
mp : 64-66°C
Rf : 0.20 (10% MeOH in $CHCl_3$)

Preparation 36-1)

Boc-D-1-Nal-OH (0.50 g), methanesulfonamide (0.18 g) DMAP (0.23 g), WSCD·HCl (0.37 g) and CH_2Cl_2 (10 ml) were reacted in a similar manner to that of Preparation 1-1) to give Boc-D-1-Nal-methanesulfonamide (0.63 g).
Rf : 0.48 (10% MeOH in $CHCl_3$)

Preparation 36-2)

Boc-D-Phe-OH (0.20 g), methanesulfonamide (79 mg) DMAP (0.11 g), WSCD·HCl (0.17 g) and DMF (4 ml) were reacted in a similar manner to that of Preparation 1-1) to give Boc-D-Phe-methanesulfonamide (0.21 g).
mp : 73-75°C
Rf : 0.80 ($CHCl_3$:MeOH:AcOH = 8:1:1, V/V)

Preparation 36-3)

Boc-D-Phe-OH (0.20 g), benzenesulfonamide (0.13 g), DMAP (0.11 g) WSCD·HCl (0.17 g) and CH_2Cl_2 (4 ml) were reacted in a similar manner to that of Preparation 1-1) to give Boc-D-Phe-benzenesulfonamide (0.32 g).
Rf : 0.83 ($CHCl_3$:MeOH:AcOH = 8:1:1, V/V)

Preparation 36-4)

Boc-D-Pya-OH (0.20 g), diethylamine (66 mg), HOBt (0.12 g), WSCD·HCl (0.17 g) and DMF (2 ml) were reacted in a similar manner to that of Preparation 1-1) to give Boc-D-Pya-diethylamide (45 mg).
mp : 133-135°C
Rf : 0.32 (EtOAc)

Preparation 37-1)

Boc-D-1-Nal-methanesulfonamide (0.60 g), 4N HCl-EtOAc (10 ml) and EtOAc (3 ml) were reacted in a similar manner to that of Preparation 1-2) to give HCl·H-D-1-Nal-methanesulfonamide.
mp : 250°C (dec.)
Rf : 0.42 ($CHCl_3$:MeOH:AcOH = 8:2:1, V/V)

Preparation 37-2)

Boc-D-Phe-methanesulfonamide (0.19 g) and 4N HCl-EtOAc (10 ml) were reacted in a similar manner to that of Preparation 1-2) to give HCl·H-D-Phe-methanesulfonamide (0.13 g).
mp : 243°C (dec.)
Rf : 0.12 ($CHCl_3$:MeOH:AcOH = 8:1:1, V/V)

Preparation 37-3)

Boc-D-Phe-benzenesulfonamide (0.30 g) and 4N HCl-EtOAc (10 ml) were reacted in a similar manner to that of Preparation 1-2) to give HCl·H-D-Phe-benzenesulfonamide (0.22 g).
Rf : 0.22 ($CHCl_3$:MeOH=AcOH = 8:1:1, V/V)
mp : 230°C (dec.)

Preparation 37-4)

Boc-D-Pya-diethylamide (45 mg) and 4N HCl-EtOAc (1 ml) were reacted in a similar manner to that of Preparation 1-2) to give 2HCl·H-D-Pya-diethylamide (41 mg).
Rf : 0.18 (10% MeOH in $CHCl_3$)

Preparation 38-1)

o-Chlorophenyl isocyanate (1.54 g), TosOH·H-1-Leu-OBzl (3.94 g) N-methylmorpholine (1.1 g) and EtOAc (50 ml) were reacted in a similar manner to that of Preparation 7 to give N-(2-chlorophenylcarbamoyl)-L-Leu-OBzl (4.30 g).
Rf : 0.86 (10% MeOH in $CHCl_3$)

Preparation 38-2)

o-Chlorophenylacetic acid (0.73 g), HCl·H-1-Leu-OBzl (1.0 g), WSCD (0.66 g) and CH_2Cl_2 (20 ml) were reacted in a similar manner to that of Preparation 1-1) to give N-(o-chlorophenylacetyl)-1-Leu-OBzl (1.4 g).
mp : 75-77°C
Rf : 0.86 (10% MeOH in $CHCl_3$)

Preparation 39

To a stirring solution of N-Boc-N-methyl-glycinal (2.0 g) and HCl·H-1-Ile-OMe (2.0 g) in MeOH was added sodium cyanoborohydride (0.87 g) at room temperature. After 30 minutes, the solvent was evaporated in vacuo and the residue was dissolved in ethyl acetate (50 ml) and washed with sodium hydrogen carbonate. The organic layer was dried over

magnesium sulfate and concentrated in vacuo. The residue was purified by a silica gel column chromatography (40 g, ethyl acetate:hexane = 1:3 ~ 3:1 as an eluent) to give N-[2-(N-Boc-N-methylamino)ethyl]-L-Ile-OMe (1.67 g).

Rf : 0.78 (EtOAc:hexane = 2:1, V/V)

Preparation 40

N-[2-(N-Boc-N-methylamino)ethyl]-1-Ile-OMe (1.60 g) and 4N HCl-EtOAc (20 ml) were reacted in a similar manner to that of Preparation 1-2) to give 2HCl·N-[2-(N-methylamino)ethyl]-1-Ile-OMe (1.40 g).

mp : 148-150°C

Rf : 0.19 (10% MeOH in $CHCl_3$).

Preparation 41

2HCl·N-[2-(N-methylamino)ethyl]-1-Ile-OMe (1.30 g) was dissolved in 24N NH_3-MeOH (20 ml) at room temperature and the solution was allowed to stand for 5 days. The solvent was evaporated in vacuo and the residue was dissolved in EtOAc (30 ml) and washed with sodium hydrogen carbonate (20 ml). The organic layer was dried over magnesium sulfate and concentrated in vacuo to give (3S)-1-methyl-3-(1-methylpropyl)-2-oxopiperazine (0.69 g).

Rf : 0.57 (10% MeOH in $CHCl_3$)

Preparation 42

To a stirring suspension of N^{α}-Boc-N^{in}-methyl-D-Trp-OH (1.0 g) and NaH (0.31 g, 60% in oil) in tetrahydrofuran was added methyl iodide (1.34 g) at room temperature. After eight days, the mixture was evaporated in vacuo and the residue was suspended in EtOAc (30 ml) and washed with 1N HCl and brine. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (20 g, 2% MeOH in $CHCl_3$ as an eluent) to give N^{α}-Boc-N^{α}-methyl-N^{in}-methyl-D-Trp-OH (0.70 g).

Rf : 0.42 (10% MeOH in $CHCl_3$)

Preparation 43

Finely powdered potassium carbonate (5.8 g) was suspended in a solution of 2-(aminomethyl)pyridine (3.0 g) and ethyl bromoacetate (3.1 ml) in dimethylformamide (30 ml). The mixture was stirred at room temperature overnight, then poured into ice water. The mixture was extracted with ethyl acetate (50 ml x 2) and the organic layer was washed with saturated sodium chloride solution (2 times), dried over magnesium sulfate, and evaporated in vacuo. The residue was purified with a silica gel column chromatography (MeOH:$CHCl_3$ = 1:99 as an eluent) to give N-(ethoxycarbonylmethyl)-N-(pyridin-2-ylmethyl)amine (2.30 g).

Rf : 0.27 (MeOH:$CHCl_3$ = 1:19)

Preparation 44

A solution of 2-[2-(t-butoxycarbonylamino)ethyl]pyridine (2 g) in dimethylformamide (10 ml) was added to a suspension of sodium hydride (0.54 g) in dimethylformamide (10 ml) at 0°C. The mixture was stirred at 0°C for 1 hour and at room temperature for 1 hour. Then a solution of ethyl bromoacetate (1.5 ml) in dimethylformamide (5 ml) was added thereto, and the mixture was stirred at room temperature for 2 hours. The solution was poured into saturated ammonium chloride (50 ml) and the mixture was extracted with ethyl acetate (30 ml x 2). The combined organic layer was washed with saturated sodium chloride solution, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified with silica gel column chromatography (MeOH:$CHCl_3$ = 1:99 as an eluent) to give 2-[2-{N-(t-butoxycarbonyl)-N-(ethoxycarbonylmethyl)amino}ethyl]pyridine.

Rf : 0.47 ($CHCl_3$:MeOH = 1:19)

Preparation 45

2-[2-{N-(t-Butoxycarbonyl)-N-(ethoxycarbonylmethyl)amino}ethyl]pyridine (439 mg) and 4NHCl-I,4-dioxane (5 ml) were reacted in a similar manner to that of Preparation 1-2) to give N-(ethoxycarbonylmethyl)-N-[2-(pyridin-2-yl)ethyl] amine dihydrochloride (400 mg).

Rf : 0.24 (MeOH:$CHCl_3$ = 1:19)

Preparation 46

N-Methyl-1-Leu-OBzl hydrochloride (600 mg), trichloromethyl chloroformate (0.54 ml), and hexamethyleneimine (877 mg) were reacted in a similar manner to those of Preparations 29-2) and 29-3) to give N-(hexahydro-1H-azepin-1-ylcarbonyl)-N-methyl-1-Leu-OBzl (515 mg).

Rf : 0.44 (n-hexane:ethyl acetate = 3:1)

Preparation 47

Boc-1-Asp(OBzl)-OH (1.0 g), 2-aminopyridine (0.35 g), HOBT (0.50 g), WSCD (0.71 g) and DMF (20 ml) were reacted in a similar manner to that of Preparation 1-1) to give Boc-1-Asp(OBzl)-2-pyridylamide.

Rf : 0.52 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Preparation 48

H-1-Asp(OBzl)-2-pyridylamide·2HCl was obtained in a similar manner to that of Preparation 1-2).

mp : 170-178°C

Rf : 0.23 (chloroform:methanol:acetic acid = 8:1:1)

Preparation 49

HCl·H-1-tert-Leu dimethylamide (0.22 g), benzyl (2R)-2-(carboxymethyl)-4-methylvalerate (0.30 g), WSCD (0.21 g) and CH_2Cl_2 (8 ml) were reacted in a similar manner to that of Preparation 1-1) to give benzyl (2R)-2-[{(1S)-1-(N,N-dimethylcarbamoyl)-2,2-dimethylpropyl}carbamoyl]methyl-4-methylvalerate (0.40 g).

Rf : 0.71 (10% MeOH in $CHCl_3$)

Example 1-1)

To a mixture of N-phenylacetyl-1-Leu-OH (0.25 g), HCl·H-D-Trp(CH3)-D-Phe-OCH3 (0.48 g) and HOBT (0.16 g) in DMF (8 ml) was added WSCD (0.19 g) under ice-bath cooling. After being stirred for 4.5 hours at the same temperature, the mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (50 ml). The solution was washed with 0.5N HCl (10 ml), saturated aqueous sodium bicarbonate (10 ml), and brine (10 ml) successively, dried over magnesium sulfate and concentrated in vacuo. The residue was triturated with ether to give the object compound (0.90 g).

mp : 185-188°C

Rf : 0.52 ($CHCl_3$:MeOH = 9:1)

Example 1-2)

To a solution of N-phenylacetyl-1-Leu-D-Trp(CH_3)-D-Phe-OCH_3 (0.85 g) in DMF (7 ml) was added 1N NaOH (1.5 ml) at 0°C. After being stirred for 20 minutes at the same temperature, the mixture was acidified with 1N HCl (2 ml) and concentrated in vacuo. The residue was dissolved in ethyl acetate (20 ml) and the solution was washed with 0.5N HCl (10 ml) and brine (10 ml). The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was triturated with ether to give the object compound (0.50 g).

mp : 177-185°C

FAB-MS m/z : 598 $[M + H]^+$

Rf : 0.52 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Example 2-1)

3-Phenylpropionic acid (33 mg), HCl·H-1-Leu-D-Trp(CH3)-D-Phe-OBzl (0.12 g), HOBT (32 mg) and WSCD (37 mg) in DMF (2 ml) were reacted in a similar manner to that of Example 1-1) to give the object compound (0.13 g).

mp : 218-220°C

Rf : 0.74 ($CHCl_3$:MeOH = 9:1)

Example 2-2)

N-(3-Phenylpropionyl)-1-Leu-D-Trp(CH3)-D-Phe-OBzl (0.1 g) in DMF (1.5 ml) was hydrolyzed with 1N NaOH (0.5

ml) in a similar manner to that of Example 1-2) to give the object compound (68 mg).

mp : 175-180°C

Rf : 0.51 ($CHCl_3$:MeOH:AcOH = 16:1:1)

FAB-MS m/z : 611 $[M + H]^+$

Example 3-1)

Cyclohexylacetic acid (31 mg), HCl·H-1-Leu-D-Trp(CH3)-D-Phe-OBzl (0.12 g), HOBT (32 mg) and WSCD (37 mg) in DMF (2 ml) was reacted in a similar manner to that of Example 1-1) to give the object compound (0.12 g).

mp : 191-194°C

Rf : 0.74 ($CHCl_3$:MeOH = 9:1)

Example 3-2)

N-Cyclohexylacetyl-1-Leu-D-Trp(CH_3)-D-Phe-OC_2H_5 (0.1 g) was reacted with 1N NaOH (0.5 ml) in DMF (1.5 ml) in a similar manner to that of Example 1-2) to give the object compound (63 mg).

mp : 225-228°C

Rf : 0.51 ($CHCl_3$:MeOH:AcOH = 16:1:1)

FAB-MS m/z : 603 $[M + H]^+$

Example 4-1)

To a solution of HCl·H-1-Leu-D-Trp(CH3)-D-Phe-OBzl (120 mg) and Et_3N (22 mg) in DMF (5 ml) was added phenyl isocyanate (26 mg) at room temperature. The mixture was stirred at the same temperature for 30 minutes. After evaporation of the solvent, the residue was dissolved in AcOEt (20 ml) and the solution was washed with 5% HCl, 1M aqueous sodium bicarbonate and saturated aqueous sodium chloride solution successively, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was crystallized from ether to give the object compound (115 mg).

mp : 222-224°C

Rf : 0.77 ($CHCl_3$:MeOH = 9:1)

Example 4-2)

N-Phenylcarbamoyl-1-Leu-D-Trp(CH_3)-D-Phe-OBzl (115 mg) in DMF (2 ml) was hydrolyzed with 1N NaOH (0.3 ml) in a similar manner to that of Example 1-2) to give the object compound (93 mg).

mp : 248-251°C

Rf : 0.60 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Example 5-1)

HCl·H-1-Leu-D-Trp(CH3)-D-Phe-OBzl (300 mg), Et_3N (50.2 mg) and cyclohexyl isocyanate (68.2 mg) in DMF (10 ml) was reacted at room temperature for 30 minutes in a similar manner to that of Example 4-1) to give the object compound (325 mg).

mp : 218-220°C

Rf : 0.67 ($CHCl_3$:MeOH = 9:1)

Example 5-2)

N-Cyclohexylcarbamoyl-1-Leu-D-Trp(CH_3)-D-Phe-OBzl (300 mg) in DMF (10 ml) was hydrolyzed with 1N NaOH (2.2 ml) at room temperature for 30 minutes in a similar manner to that of Example 1-2) to give the object compound (246 mg).

mp : 219-221°C

Rf : 0.52 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Example 6-1)

N-Phenylacetyl-1-Leu-D-Trp(CH3)-OH (0.20 g), HOBT (72 mg), WSCD (83 mg) and NMM (54 mg) were reacted in a similar manner to that of Preparation 3-3) to give the object compound (0.21 g).

mp : 130-137°C
Rf : 0.51 ($CHCl_3$:MeOH = 9:1)
FAB-MS m/z : 626 $[M + H]^+$

Example 6-2)

N-Phenylacetyl-1-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5·HCl (0.15 g) in DMF (2 ml) was reacted with 1N-NaOH (1 ml) at 0°C for 20 minutes in a similar manner to that of Example 1-2) to give the object compound (102 mg).
mp : 205°C (dec.)
Rf : 0.33 ($CHCl_3$:MeOH:AcOH = 8:1:1)
FAB-MS m/z : 598 $[M + H]^+$

Example 7-1)

2HCl·H-1-Leu-D-Trp(CH3)-D-Pya-OC_2H_5 (350 mg), Et_3N (122 mg) and cyclohexyl isocyanate (91 mg) in DMF (10 ml) was reacted at room temperature for 30 minutes in a similar manner to that of Example 4-1) to give the object compound (284 mg).
mp : 216-218°C
Rf : 0.61 ($CHCl_3$:MeOH = 9:1)

Example 7-2)

N-Cyclohexylcarbamoyl-1-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5 (230 mg) in MeOH (10 ml) was reacted with 1N NaOH (1.6 ml) at room temperature for 1 hour in a similar manner to that of Example 1-2) to give the object compound (125 mg).
mp : 207-210°C
Rf : 0.45 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 8

To a solution of N-cyclohexylcarbamoyl-L-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5 (920 mg) in DMF (20 ml) was added 1N NaOH (7.3 ml) at room temperature. After 10 minutes, 1N HCl (8.5 ml) was added and the solution was evaporated in vacuo. The residue was dissolved in 1N HCl (50 ml) and water (200 ml), and applied to a column of "Diaion HP-20" (trademark, made by Mitsubishi Chemical Industries) eluting with MeOH (300 ml). After the eluate was concentrated in vacuo, the residue (750 mg) was dissolved in 1N NaOH (1.24 ml) and lyophilized to give the object compound as a white powder (728 mg).
Rf : 0.45 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 9

N-[(1S)-2,2-Dimethyl-1-(N,N-dimethylcarbamoyl)-propyl]carbamoyl-1-Leu-OH (0.28 g), H-D-Trp(CH_3)-D-Pya-OC_2H_5·2HCl (0.41 g), HOBT (0.14 g), WSCD (0.16 g) and TEA (89 mg) were reacted in DMF (7 ml) in a similar manner to that of Example 1-1) to give the object compound (0.40 g).
mp : 141-145°C
Rf : 0.43 ($CHCl_3$:MeOH = 9:1)
NMR ($CDCl_3$, δ): 0.82 (3H, d, J=6.0Hz), 0.87 (3H, d, J=6.0Hz), 1.15 (3H, t, J=6.0Hz), 1.35 (2H, t, J=6.0Hz), 1.65 (1H, m), 2.58 (3H, s), 3.06 (3H, s), 3.1-3.3 (4H, m), 3.70 (3H, s), 4.06 (2H, q, J=6.0Hz), 4.34 (1H, q, J=6.0Hz), 4.75 (1H, d, J=10.0Hz), 4.90 (1H, q, J=6.0Hz), 5.13 (1H, q, J=6.0Hz), 6.20 (1H, d, J=10.0Hz), 6.48 (1H, d, J=8.0Hz), 6.58 (1H, d, J=7.5Hz), 6.90 (1H, s), 6.95-7.30 (6H, m), 7.56 (1H, td, J=7.5, 2.0Hz), 7.65 (1H, d, J=7.5Hz), 7.98 (1H, d, J=8.0Hz), 8.34 (1H, d, J=5.0Hz)

Example 10

(2S)-2-[N-[(1S)-2,2-Dimethyl-1-(N,N-dimethylcarbamoyl)propyl]carbamoyloxy]-4-methylvaleric acid (0.15 g), H-D-Trp(CH_3)-D-Pya-OC_2H_5·2HCl (0.24 g), HOBT (77 mg), WSCD (88 mg) and NMM (53 mg) were reacted in DMF (4 ml) in a similar manner to that of Example 1-1) to give the object compound (0.33 g).
Rf : 0.73 ($CHCl_3$:MeOH = 9:1)

Example 11

N-(Hexahydro-1H-azepin-1-ylcarbonyl)-1-Leu-OH (1.51 g), 2HCl·H-D-Trp(CH3)-D-Pya-OC_2H_5 (2.50 g), WSCD (997 mg), HOBT (868 mg) and NMM (541 mg) were reacted in DMF (60 ml) in a similar manner to that of Example 1-1) to give the object compound (2.16 g).

Rf : 0.34 (ethyl acetate)

NMR ($CDCl_3$, δ): 0.82 (3H, d, J=6.0Hz), 0.84 (3H, d, J=6.0Hz), 1.18 (3H, t, J=7.5Hz), 1.3-1.8 (11H, m), 3.1-3.5 (7H, m), 3.68 (3H, s), 4.10 (2H, q, J=7.5 Hz), 4.10 (1H, br), 4.7-4.9 (3H, m), 6.68 (1H, d, J=8.0Hz), 6.95 (1H, s), 7.0-7.3 (5H, m), 7.5 (1H, td, J=8.0, 2.0Hz), 7.64 (2H, t, J=8.0Hz), 8.28 (1H, d, J=5.0Hz)

Example 12

(2R)-2-(Hexahydro-1H-azepin-1-ylcarbonylmethyl)-4-methylvaleric acid (982 mg). 2HCl·H-D-Trp(CH3)-D-Pya-OC_2H_5 (1.54 g), WSCD (612 mg), HOBT (532 mg) and TEA (332 mg) were reacted in DMF (30 ml) in a similar manner to that of Example 1-1) to give the object compound (1.41 g).

Rf : 0.43 ($CHCl_3$:MeOH = 9:1)

Example 13

N-(Octahydroazocin-1-ylcarbonyl)-1-Leu-OH (191 mg), 2HCl·H-D-Trp(CH3)-D-Pya-OC_2H_5 (300 mg), WSCD (120 mg), HOBT (104 mg) and TEA (65 mg) were reacted in DMF (20 ml) in a similar manner to that of Example 1-1) to give the object compound (340 mg).

Rf : 0.60 ($CHCl_3$:MeOH = 9:1)

Example 14

2HCl·H-1-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5 (4.35 g), hexahydro-1H-azepin-1-ylcarbonyl chloride (1.29 g) and TEA (2.33 g) were reacted in DMF (60 ml) in a similar manner to that of Example 4-1) to give the object compound (1.95 g).

Rf : 0.44 ($CHCl_3$:MeOH = 9:1)

Example 15

To a solution of N-(hexahydro-1H-azepin-1-ylcarbonyl)-1-Leu-D-Trp(CH3)-D-Pya-OC_2H_5 (37 g) in ethanol (740 ml) was added 1N NaOH (146 ml) under ice-bath cooling. After stirring for 30 minutes, 1N HCl (150 ml) was added to the reaction mixture, and the solvent was removed by evaporation in vacuo. The residue was dissolved in 1N HCl (500 ml) and water (5000 ml) and applied to a column chromatography using non-ionic adsorption resin "Diaion HP-20" (3 ℓ), which was eluted with methanol (10 ℓ). After the eluent was concentrated in vacuo, the residue was crystallized from n-hexane to give the object compound (34.1 g).

mp : 113-118°C

Rf : 0.34 ($CHCl_3$:MeOH:AcOH = 8:1:1)

NMR ($CDCl_3$, δ): 0.89 (6H, d, J=5.0Hz), 1.32-1.80 (11H, m), 3.11 (2H, d, J=6.0Hz), 3.16-3.53 (6H, m), 3.78 (3H, s), 4.20 (1H, br), 4.22-4.48 (1H, m), 4.59 (1H, q, J=6.0Hz), 4.77 (1H, q, J=7.0Hz), 4.90 (1H, d, J=7.5Hz), 7.01 (1H, s), 7.04-7.52 (7H, m), 7.71 (1H, d, J=7.0Hz), 7.82 (1H, t, J=8.0Hz), 8.48 (1H, d, J=5.0Hz)

Example 16

N-(Hexahydro-1H-azepin-1-ylcarbonyl)-1-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5 (1.35 g) and 1N NaOH (6.4 ml) were reacted in ethanol (30 ml) in a similar manner to that of Example 8 to give the object compound (1.08 g).

Rf : 0.44 ($CHCl_3$:MeOH:AcOH = 8:1:1)

NMR (DMSO-d_6, δ): 0.74 (3H, d, J=3.0Hz), 0.79 (3H, d, J=3.0Hz), 1.08-1.67 (11H, m), 2.72-3.12 (3H, m), 3.18-3.38 (5H, m), 3.69 (3H, s), 4.09-4.25 (2H, m), 4.28-4.43 (1H, m), 6.08 (1H, d, J=8.5Hz), 6.92-7.15 (4H, m), 7.25 (1H, d, J=8.0Hz), 7.32 (1H, d, J=8.0Hz), 7.49-7.62 (2H, m), 7.69 (1H, d, J=8.5Hz), 8.03 (1H, d, J=9.0Hz), 8.40 (1H, d, J=4.0Hz)

Example 17

N-[N-[(1S)-2,2-Dimethyl-1-(N,N-dimethylcarbamoyl)propyl]carbamoyl]-1-Leu-D-Trp(CH3)-D-Pya-OC_2H_5 (0.31 g) and 1N NaOH (1.5 ml) were reacted in DMF in a similar manner to that of Example 8 to give the object compound

(0.25 g).

Rf : 0.31 ($CHCl_3$:MeOH:AcOH = 8:1:1)

NMR (DMSO-d_6, δ): 0.66 (6H, d, J=6.0Hz), 0.88 (9H, s), 1.0-1.3 (3H, m), 2.7-3.3 (4H, m), 2.8 (3H, s), 3.08 (3H, s), 3.68 (3H, s), 4.08 (1H, q, J=6.0Hz), 4.20 (1H, q, J=5.0Hz), 4.38 (1H, m), 4.50 (1H, d, J=9.0Hz), 6.37 (1H, d, J=9.0Hz), 6.48 (1H, d, J=7.5Hz), 6.9-7.15 (4H, m), 7.2 (1H, d, J=7.5Hz), 7.3 (1H, d, J=7.5Hz), 7.45-7.6 (2H, m), 7.66 (1H, d, J=7.5Hz), 8.28 (1H, d, J=8.0Hz), 8.38 (1H, d, J=4.0Hz)

Example 18

N-[(2S)-2-[N-[(1S)-2,2-dimethyl-1-(N,N-dimethylcarbamoyl)propyl]carbamoyloxy]-4-methylvaleryl]-D-Trp(CH_3)-D-Pya-OC_2H_5 (0.30 g) and 1N NaOH (1.3 ml) were reacted in DMF (2.6 ml) in a similar manner to that of Example 8 to give the object compound (0.26 g).

Rf : 0.20 ($CHCl_3$:MeOH:AcOH = 8:1:1)

NMR (DMSO-d_6, δ): 0.78 (6H, d, J=6.5Hz), 0.88 (9H, s), 1.2-1.6 (3H, m), 2.7-3.4 (4H, m), 2.83 (3H, s), 3.05 (3H, s), 3.66 (3H, s), 4.16 (1H, q, J=6.0Hz), 4.34-4.48 (2H, m), 4.75 (1H, q, J=3.0Hz), 6.9-7.7 (10H, m), 8.16 (1H, d, J=10.0Hz), 8.40 (1H, d, J=4.0Hz)

Example 19

N-[(2R)-2-(Hexahydro-1H-azepin-1-ylcarbonylmethyl)-4-methylvaleryl]-D-Trp(CH_3)-D-Pya-OC_2H_5 (1.10 g) and 1N NaOH (5.2 ml) were reacted in ethanol (20 ml) in a similar manner to that of Example 8 to give the object compound (783 mg).

Rf : 0.49 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 20

N-(Octahydroazocin-1-ylcarbonyl)-1-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5 (300 mg) and 1N NaOH (2.4 ml) were reacted in ethanol (10 ml) in a similar manner to that of Example 8 to give the object compound (210 mg).

Rf : 0.68 ($CHCl_3$:MeOH:AcOH = 8:2:1)

NMR (DMSO-d_6, δ): 0.75 (6H, d, J=5.5Hz), 1.02-1.65 (16H, m), 2.72-3.32 (5H, m), 3.68 (3H, s), 4.08-4.26 (2H, m), 4.29-4.45 (1H, m), 5.93 (1H, d, J=8.5Hz), 6.92-7.18 (4H, m), 7.13 (1H, d, J=8.0Hz), 7.32 (1H, d, J=9.0Hz), 7.48-7.69 (3H, m), 7.97 (1H, d, J=9.0Hz), 8.38 (1H, d, J=4.5Hz)

Example 21

To a solution of N-(hexahydro-1H-azepin-1-ylcarbonyl)-1-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5 (800 mg) in ethanol (10 ml) was added 4N hydrogen chloride in ethyl acetate solution (0.63 ml) under ice-bath cooling. After stirring for 5 minutes at the same temperature, the solution was concentrated in vacuo to give the object compound (828 mg).

Rf : 0.64 ($CHCl_3$:MeOH = 9:1)

NMR (DMSO-d_6, δ): 0.71 (3H, d, J=5.0Hz), 0.77 (3H, d, J=5.0Hz), 1.14 (3H, t, J=6.0Hz), 1.15-1.66 (11H, m), 2.82 (1H, q, J=11.0Hz), 3.08-4.18 (8H, m), 3.72 (3H, s), 4.08 (2H, q, J=7.5Hz), 4.32-4.48 (1H, m), 4.63-4.80 (1H, m), 6.13 (1H, br), 7.02 (2H, t, J=7.0Hz), 7.13 (1H, t, J=7.5Hz), 7.37 (1H, d, J=8.0Hz), 7.57 (1H, d, J=7.5Hz), 7.82 (2H, t, J=7.0Hz), 8.22-8.42 (2H, m), 8.78 (2H, d, J=5.0Hz)

Example 22

N-[(2R)-2-hexahydro-1H-azepin-1-ylcarbonylmethyl)-4-methylvaleryl]-D-Trp(CH3)-D-Pya-OC_2H_5 (300 mg), 4N hydrogen chloride in ethyl acetate (0.36 ml) were reacted in ethanol (10 ml) in a similar manner to that of Example 21 to give the object compound (298 mg).

Rf : 0.43 ($CHCl_3$:MeOH = 9:1)

The object compounds in Examples 23 to 69 could be obtained by reacting the corresponding starting compounds (II) and (III) in a similar manner to that of Example 1-1).

The physico-chemical properties of these object compounds are provided hereinbelow.

Example 23

mp : 193-195°C

Rf : 0.49 ($CHCl_3$:MeOH = 9:1)

Example 24

mp : 186-189°C
Rf : 0.62 ($CHCl_3$:MeOH = 9:1)

Example 25

mp : 181-183°C
Rf : 0.56 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 26

Rf : 0.49 ($CHCl_3$:MeOH = 9:1)

Example 27

Rf : 0.77 ($CHCl_3$:MeOH = 9:1)

Example 28

Rf : 0.77 ($CHCl_3$:MeOH = 9:1)

Example 29

Rf : 0.57 ($CHCl_3$:MeOH = 9:1)

Example 30

Rf : 0.56 ($CHCl_3$:MeOH = 9:1)

Example 31

mp : 184-185°C
Rf : 0.54 ($CHCl_3$:MeOH = 9:1)

Example 32

Rf : 0.77 ($CHCl_3$:MeOH = 9:1)

Example 33

Rf : 0.43 ($CHCl_3$:MeOH = 9:1)

Example 34

Rf : 0.53 ($CHCl_3$:MeOH = 9:1)

Example 35

Rf : 0.36 ($CHCl_3$:MeOH = 9:1)

Example 36

mp : 79-81°C
Rf : 0.60 ($CHCl_3$:MeOH:AcOH=16:1:1)

Example 37

mp : 69-71°C
Rf : 0.43 ($CHCl_3$:MeOH=9:1)

Example 38

mp : 54-55°C
Rf : 0.41 ($CHCl_3$:MeOH = 9:1)

Example 39

mp : 100-105°C
Rf : 0.41 ($CHCl_3$:MeOH = 9:1)

Example 40

Rf : 0.53 ($CHCl_3$:MeOH = 9:1)

Example 41

Rf : 0.55 ($CHCl_3$:MeOH = 9:1)

Example 42

mp : 62-68°C
Rf : 0.52 ($CHCl_3$:MeOH = 9:1)

Example 43

mp : 60-67°C
Rf : 0.51 ($CHCl_3$:MeOH = 9:1)

Example 44

mp : 70-75°C
Rf : 0.58 ($CHCl_3$:MeOH = 9:1)

Example 45

mp : 80-83°C
Rf : 0.53 ($CHCl_3$:MeOH = 9:1)

Example 46

Rf : 0.55 ($CHCl_3$:MeOH = 9:1)

Example 47

Rf : 0.48 ($CHCl_3$:MeOH = 9:1)

Example 48

mp : 140-142°C
Rf : 0.43 ($CHCl_3$:MeOH = 9:1)

Example 49

Rf : 0.52 ($CHCl_3$:MeOH = 9:1)

Example 50

mp : 135-138°C
Rf : 0.31 ($CHCl_3$:MeOH = 9:1)

Example 51

mp : 185-188°C
Rf : 0.50 ($CHCl_3$:MeOH = 9:1)

Example 52

mp : 170-178°C
Rf : 0.48 ($CHCl_3$:MeOH = 9:1)

Example 53

mp : 194-196°C
Rf : 0.45 ($CHCl_3$:MeOH = 9:1)

Example 54

mp : 166-167°C
Rf : 0.70 ($CHCl_3$:MeOH = 9:1)

Example 55

mp : 110-115°C
Rf : 0.59 ($CHCl_3$:MeOH = 9:1)

Example 56

mp : 79-80°C
Rf : 0.79 ($CHCl_3$:MeOH = 9:1)

Example 57

mp : 77-79°C
Rf : 0.52 ($CHCl_3$:MeOH = 9:1)

Example 58

Rf : 0.36 ($CHCl_3$:MeOH = 9:1)

Example 59

Rf : 0.53 ($CHCl_3$:MeOH = 9:1)

Example 60

Rf : 0.53 ($CHCl_3$:MeOH = 9:1)

Example 61

mp : 185-188°C
Rf : 0.53 ($CHCl_3$:MeOH = 9:1)

Example 62

mp : 170-175°C
Rf : 0.58 ($CHCl_3$:MeOH = 9:1)

Example 63

Rf : 0.71 ($CHCl_3$:MeOH = 9:1)

Example 64

mp : 183-190°C
Rf : 0.60 ($CHCl_3$:MeOH = 9:1)

Example 65

Rf : 0.70 ($CHCl_3$:MeOH = 9:1)

Example 66

Rf : 0.79 ($CHCl_3$:MeOH = 9:1)

Example 67

mp : 159-161°C
Rf : 0.62 ($CHCl_3$:MeOH = 9:1)

Example 68

Rf : 0.51 ($CHCl_3$:MeOH = 9:1)

Example 69

mp : 148-150°C
Rf : 0.78 ($CHCl_3$:MeOH = 9:1)

Example 70

To a solution of KCl·H-1-Ile-OMe (135 mg) and Et_3N (50.2 mg) in dry toluene (10 ml) was added trichloromethyl chloroformate (0.055 ml). After the solution was refluxed for 30 minutes, it was concentrated under reduced pressure. The resulting residue was dissolved in DMF (10 ml) and a mixture of HCl·H-1-Leu-D-Trp(CH_3)-D-Phe-OBzl (300 mg) and Et_3N (50.2 mg) in DMF (10 ml) was added to the solution at room temperature. After the reaction mixture was stirred for 1 hour, the solvent was removed in vacuo. The resulting residue was dissolved in ethyl acetate (30 ml) and the solution was washed with 5% HCl, 1M sodium bicarbonate and saturated sodium chloride solution successively, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was crystallized from ether to give the object compound (324 mg).

mp : 184-186°C
Rf : 0.80 ($CHCl_3$:MeOH = 9:1)

Example 71

To a mixture of HCl·H-1-Leu-D-Trp(CH_3)-D-Phe-OBzl (0.12 g), 4-pyridylacetic acid (38 mg) and NMM (24 mg) in DMF (2 ml) was added WSCD (37 mg) under ice-bath cooling. After being stirred for 3 hours at room temperature, the

mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate. The solution was washed with 0.5N HCl, water, saturated sodium bicarbonate and water successively, dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with ether to give the object compound (107 mg).

mp : 122-125°C

Rf : 0.46 ($CHCl_3$:MeOH = 9:1)

The object compounds in Examples 72 to 80 could be obtained by reacting the corresponding starting compounds (I-a) and (IV) in a similar manner to that of Example 71.

The physico-chemical properties of these object compounds are provided hereinbelow.

Example 72

mp : 105-110°C

Rf : 0.50 ($CHCl_3$:MeOH = 9:1)

Example 73

mp : 98-108°C

Rf : 0.65 ($CHCl_3$:MeOH = 9:1)

Example 74

mp : 173-175°C

Rf : 0.84 ($CHCl_3$:MeOH = 9:1)

Example 75

mp : 196-199°C

Rf : 0.79 ($CHCl_3$:MeOH = 9:1)

Example 76

mp : 139-141°C

Rf : 0.60 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 77

mp : 90-96°C

Rf : 0.36 ($CHCl_3$:MeOH = 9:1)

Example 78

mp : 206-209°C

Rf : 0.45 ($CHCl_3$:MeOH = 9:1)

Example 79

mp : 124-128°C

Rf : 0.56 ($CHCl_3$:MeOH = 9:1)

Example 80

Rf : 0.64 ($CHCl_3$:MeOH = 9:1)

Example 81

To a mixture of benzylsulfonyl chloride (0.18 g) and HCl·H-1-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5 (0.50 g) in DMF (10 ml) was added Et_3N (0.42 ml) at 0°C. After the reaction was completed, the solution was evaporated to dryness in vacuo. The residue was dissolved in ethyl acetate, and the solution was washed with 0.5N HCl, dried over magnesium

sulfate and concentrated in vacuo. The residual solid was triturated with ether to give the object compound (0.29 g).

mp : 98-100°C

Rf : 0.51 ($CHCl_3$:MeOH = 9:1)

Example 82

Morpholinocarbonyl chloride (108 mg), 2HCl·H-1-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5 (350 mg) and Et_3N (122 mg) were reacted in a similar manner to that of Example 81 to give the object compound.

Rf : 0.45 ($CHCl_3$:MeOH = 9:1)

The object compounds in Examples 83 to 89 could be obtained by reacting the corresponding starting compound (I-a) with the isocyanate compound (IV) in a similar manner to that of Example 4-1).

The physico-chemical properties of these object compounds are provided hereinbelow.

Example 83

mp : 222-223°C

Rf : 0.79 ($CHCl_3$:MeOH = 9:1)

Example 84

mp : 198-204°C

Rf : 0.49 ($CHCl_3$:MeOH = 9:1)

Example 85

mp : 205-206°C

Rf : 0.46 ($CHCl_3$:MeOH = 9:1)

Example 86

mp : 216-218°C

Rf : 0.45 ($CHCl_3$:MeOH = 9:1)

Example 87

mp : 188-202°C

Rf : 0.53 ($CHCl_3$:MeOH = 9:1)

Example 88

mp : 167-172°C

Rf : 0.53 ($CHCl_3$:MeOH = 9:1)

Example 89

mp : 163-167°C

Rf : 0.53 ($CHCl_3$:MeOH = 9:1)

Example 90

To a mixture of N-cyclohexylcarbamoyl-1-Leu-D-Trp(CH_3)-OH (0.40 g), H-D-4Pya-OC_2H_5·2HCl (0.26 g), NMM (0.10 g) and HOBT (0.14 g) in DMF (8 ml) was added WSCD (0.16 g) under ice-bath cooling. After being stirred at room temperature, the mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate. The solution was washed with 0.5N HCl, water, saturated sodium bicarbonate and water successively, dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with ether to give the object compound (0.45 g).

mp : 182-186°C

Rf : 0.32 ($CHCl_3$:MeOH:AcOH = 16:1:1)

The object compounds in Examples 91 to 95 could be obtained by reacting the corresponding starting compounds

(V) and (VI) in a similar manner to that of Example 90.

The physico-chemical properties of these object compounds are provided hereinbelow.

Example 91

mp : 170-173°C
Rf : 0.43 ($CHCl_3$:MeOH = 9:1)

Example 92

mp : 181-182°C
Rf : 0.71 ($CHCl_3$:MeOH = 9:1)

Example 93

mp : 197-198°C
Rf : 0.70 ($CHCl_3$:MeOH = 9:1)

Example 94

mp : 115-123°C
Rf : 0.74 ($CHCl_3$:MeOH = 9:1)

Example 95

mp : 148-156°C
Rf : 0.52 ($CHCl_3$:MeOH:AcOH = 16:1:1)

The object compounds in Examples 96 to 141 could be obtained by hydrolyzing the corresponding ethyl ester compound (I-c) with an aqueous NaOH in a similar manner to that of Example 1-2), 8 or 15.

The physico-chemical properties of these object compounds are provided hereinbelow.

Example 96

mp : 167-170°C
Rf : 0.44 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 97

mp : 173-178°C
Rf : 0.62 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 98

mp : 150-155°C
Rf : 0.25 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 99

Rf : 0.51 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 100

Rf : 0.69 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 101

Rf : 0.66 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 102

Rf : 0.78 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 103

Rf : 0.57 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 104

Rf : 0.52 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 105

Rf : 0.72 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 106

Rf : 0.56 ($CHCl_3$:MeOH:AcOH = 20:20:1)

Example 107

Rf : 0.32 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 108

Rf : 0.31 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 109

mp : 150-155°C
Rf : 0.29 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 110

Rf : 0.31 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 111

Rf : 0.31 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 112

Rf : 0.33 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 113

Rf : 0.33 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 114

Rf : 0.34 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 115

Rf : 0.32 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 116

Rf : 0.33 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 117

Rf : 0.38 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 118

Rf : 0.34 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 119

Rf : 0.35 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 120

Rf : 0.33 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 121

Rf : 0.31 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 122

Rf : 0.33 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 123

Rf : 0.28 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 124

Rf : 0.32 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 125

Rf : 0.29 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 126

Rf : 0.33 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 127

Rf : 0.29 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 128

Rf : 0.33 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 129

Rf : 0.31 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 130

Rf : 0.37 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 131

Rf : 0.46 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 132

Rf : 0.24 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 133

Rf : 0.38 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 134

Rf : 0.29 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 135

Rf : 0.32 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 136

Rf : 0.31 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 137

Rf : 0.33 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 138

Rf : 0.53 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 139

Rf : 0.57 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 140

Rf : 0.50 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 141

Rf : 0.62 ($CHCl_3$:MeOH:AcOH = 8:1:1)
NMR (DMSO-d_6, δ): 0.54 (3H, d, J=6.0Hz), 0.64 (3H, d, J=6.0Hz), 0.72 (-1.02 (2H, m), 1.10-1.72 (13H, m), 2.22-2.32 (1H, m), 2.55-2.82 (2H, m), 2.93-3.60 (6H, m), 3.68 (3H, s), 4.04-4.10 (1H, m), 4.24-4.40 (1H, m), 6.94-7.18 (4H, m), 7.20-7.42 (2H, m), 7.46-7.68 (3H, m), 8.30 (1H, d, J=7.5Hz), 8.41 (1H, d, J=4.0Hz)

The object compounds in Examples 142 to 147 could be obtained by hydrolyzing the corresponding benzyl ester compound (I-c) with an aqueous NaOH in a similar manner to that of Example 1-2), 8 or 15.

The physico-chemical properties of these object compounds are provided hereinbelow.

Example 142

mp : 120-124°C
Rf : 0.85 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 143

mp : 220-236°C
Rf : 0.16 ($CHCl_3$:MeOH:AcOH = 16:1:1)
FAB MS m/z : 598 $[M + H]^+$

Example 144

mp : 214-218°C
Rf : 0.20 ($CHCl_3$:MeOH:AcOH:16:1:1)
FAB MS m/z : 598 $[M + H]^+$

Example 145

mp : 174-180°C
Rf : 0.32 ($CHCl_3$:MeOH:AcOH = 16:1:1)
FAB MS m/z : 598 $[M + H]^+$

Example 146

mp : 194°C (dec.)
Rf : 0.51 ($CHCl_3$:MeOH:AcOH = 16:1:1)
FAB MS m/z : 711 $[M + H]^+$

Example 147

mp : 195°C (dec.)
Rf : 0.51 ($CHCl_3$:MeOH:AcOH = 16:1:1)
FAB MS m/z : 711 $[M + H]^+$

The object compounds in Examples 148 to 153 could be obtained by hydrolyzing the corresponding ethyl ester compound (I-c) with an aqueous NaOH in a similar manner to that of Example 1-2), 8 or 15.

The physico-chemical properties of these object compounds are provided hereinbelow.

Example 148

mp : 127-145°C
Rf : 0.29 ($CHCl_3$:MeOH:AcOH = 8:2:1)
FAB MS m/z : 672 $[M + H]^+$

Example 149

Rf : 0.36 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 150

Rf : 0.38 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 151

Rf : 0.35 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 152

Rf : 0.32 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 153

Rf : 0.45 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 154

Isopropylcarbamoyl-1-Leu-D-Trp(CH_3)-D-Phe-OBzl (60 mg) was reacted with 1N NaOH (2 ml) in DMF (2 ml) at room temperature for 30 minutes in a similar manner to that of Example 1-2) to give the object compound (48 mg).

mp : 211-213°C

Rf : 0.54 ($CHCl_3$:MeOH:AcOH = 16:1:1)

The object compounds in Examples 155 to 162 could be obtained by hydrolyzing the corresponding ethyl ester compound (I-c) with an aqueous NaOH in a similar manner to that of Example 8.

The physico-chemical properties of these object compounds are provided hereinbelow.

Example 155

mp : >250°C

Rf : 0.12 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Example 156

mp : >250°C

Rf : 0.10 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Example 157

mp : >250°C

Rf : 0.12 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Example 158

mp : >250°C

Rf : 0.13 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Example 159

mp : 245°C (dec.)

Rf : 0.13 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Example 160

mp : >250°C

Rf : 0.13 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Example 161

Rf : 0.37 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 162

Rf : 0.33 ($CHCl_3$:MeOH:AcOH = 8:1:1)

The object compounds in Examples 163 to 165 could be obtained by hydrolyzing the corresponding benzyl ester compound (I-c) with an aqueous NaOH in a similar manner to that of Example 1-2) or 15.

The physico-chemical properties of those object compounds are provided hereinbelow.

Example 163

mp : 171-174°C

Rf : 0.51 ($CHCl_3$:MeOH:AcOH = 16:1:1)

FAB MS m/z : 563 $[M + H]^+$

Example 164

mp : 165-175°C
Rf : 0.51 ($CHCl_3$:MeOH:AcOH = 16:1:1)
FAB MS m/z : 549 $[M + H]^+$

Example 165

mp : 132-136°C
Rf : 0.31 ($CHCl_3$:MeOH:28% aq. ammonia = 65:25:4)

Example 166

N-Phenylacetyl-1-Leu-D-Trp(CH3)-D-4-thiazolylalanine·HCl was hydrolyzed with 1N NaOH in a similar manner to that of Example 1-2) to give the object compound.
mp : 112-116°C
Rf : 0.33 ($CHCl_3$:MeOH:AcOH = 8:1:1)
FAB MS m/z : 604 $[M + H]^+$

Example 167

N-Cyclohexyloxycarbonyl-1-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5 (0.25 g) was hydrolyzed with 1N NaOH (1 ml) in DMF (3 ml) in a similar manner to that of Example 8 to give the object compound (0.16 g).
Rf : 0.36 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Reference Example 1

N-Phenylacetyl-1-Leu-D-Trp(CHO)-D-Phe-OPac (0.20 g) was dissolved in a mixture of DMF (2 ml) and acetic acid (2 ml), and Zn powder (0.20 g) was added to the mixture at room temperature. After being stirred for 3 hours at the same temperature, the mixture was filtered and concentrated in vacuo. The residue was dissolved in ethyl acetate and the solution was washed with 0.5N HCl, dried over magnesium sulfate and concentrated in vacuo. The residue was triturated with ethyl ether to give the object compound (0.16 g).
mp : 230°C (dec.)
Rf : 0.51 ($CHCl_3$:MeOH:AcOH = 16:1:1)
FAB-MS m/z : 611

Example 168

A solution of N-[1(S)-methoxycarbonyl-2(S)-methylbutylcarbamoyl]-1-Leu-D-Trp(CH_3)-D-Phe-OBzl (270 mg) in DMF (20 ml) and water (1 ml) was hydrogenated over 10% Pd-C (50 mg) at 3 atmospheric pressure of hydrogen for 1 hour at room temperature. After the solution was filtered and the filtrate was concentrated in vacuo, the residue was crystallized from ethyl acetate and ether to give the object compound (198 mg).
mp : 210-212°C
Rf : 0.48 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Example 169

N-[1(S)-Methoxycarbonyl-2(S)-methylbutylcarbamoyl]-L-Leu-D-Trp(CH_3)-D-Phe-OBzl (70 mg) and 1N NaOH (1 ml) in DMF (2 ml) were reacted in a similar manner to that of Example 1-2) to give the object compound (50 mg).
mp : 221-225°C
Rf : 0.42 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Example 170

To a solution of cyclohexanol (0.10 ml) in tetrahydrofuran (3 ml) was added trichloromethyl chloroformate (0.13 ml) at room temperature. This solution was refluxed for 11 hours and the solvent was evaporated at atmospheric pressure in vacuo. The residual oil was dissolved in DMF (10 ml), and 2HCl·H-Leu-D-Trp(CH_3)-D-Pya-OEt (0.50 g) was added. The mixture was adjusted to about pH 7 with NMM (Ca. 0.2 g). After 10 minutes, the solvent was evaporated

in vacuo, and the residue was dissolved in ethyl acetate (20 ml). This solution was washed with 1N HCl, saturated sodium bicarbonate and brine successively, dried over magnesium sulfate and then concentrated in vacuo. The residual solid was triturated with ethyl ether to give the object compound (0.29 g).

mp : 128-130°C

Rf : 0.50 ($CHCl_3$:MeOH = 9:1)

Example 171

To a solution of N-phenylacetyl-1-Leu-D-Trp(CH_3)-D-His(Tos)-OBzl (78 mg) in DMF (2 ml) was added pyridine hydrochloride (0.15 g) at room temperature. After stirring for 2 hours, the solvent was removed by evaporation in vacuo and the residue was dissolved in ethyl acetate (20 ml). This solution was washed with 1M sodium bicarbonate (10 ml), dried over magnesium sulfate and evaporated in vacuo to give the object compound (45 mg).

mp : 118-126°C

Rf : 0.28 ($CHCl_3$:MeOH = 9:1)

Example 172

Boc-D-phenylglycyl-1-Leu-D-Trp(CH_3)-D-Phe-OH (0.1 g), trifluoroacetic acid (1.5 ml) and anisole (0.2 ml) were reacted in a similar manner to that of Preparation 1-2) to give the object compound (90 mg).

mp : 135-165°C

Rf : 0.20 ($CHCl_3$:MeOH:AcOH = 16:1:1)

FAB-MS m/z : 612 $[M + H]^+$

Example 173

Boc-1-Phenylglycyl-1-Leu-D-Trp(CH_3)-D-Phe-OH (0.11 g), TFA (1.5 ml) and anisole (0.2 ml) were reacted in a similar manner to that of Preparation 1-2) to give the object compound (107 mg).

mp : 145-170°C

Rf : 0.20 ($CHCl_3$:MeOH:AcOH = 16:1:1)

FAB-MS m/z : 612 $[M + H]^+$

The object compounds in Examples 174 to 202 were obtained by reacting the corresponding starting compounds (II) and (III) in a similar manner to that of Example 1-1), preferably in the presence of a suitable base.

The physico-chemical properties of these object compounds are provided hereinbelow.

Example 174

Rf : 0.52 ($CHCl_3$:MeOH = 9:1)

Example 175

Rf : 0.61 ($CHCl_3$:MeOH = 9:1)

Example 176

Rf : 0.80 ($CHCl_3$:MeOH = 9:1)

Example 177

mp : 192-193°C

Rf : 0.67 ($CHCl_3$:MeOH = 9:1)

Example 178

mp : 155-160°C

Rf : 0.82 ($CHCl_3$:MeOH = 9:1)

Example 179

Rf : 0.72 ($CHCl_3$:MeOH = 9:1)

Example 180

Rf : 0.34 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 181

mp : 180-185°C
Rf : 0.50 ($CHCl_3$:MeOH = 9:1)

Example 182

mp : 125-127°C
Rf : 0.46 ($CHCl_3$:MeOH = 9:1)

Example 183

Rf : 0.78 ($CHCl_3$:MeOH = 9:1)

Example 184

mp : 143-146°C
Rf : 0.46 ($CHCl_3$:MeOH = 9:1)

Example 185

Rf : 0.40 ($CHCl_3$:MeOH = 9:1)

Example 186

mp : 180°C
Rf : 0.44 ($CHCl_3$:MeOH = 9:1)

Example 187

mp : 138-140°C
Rf : 0.42 ($CHCl_3$:MeOH = 9:1)

Example 188

Rf : 0.37 ($CHCl_3$:MeOH = 9:1)

Example 189

Rf : 0.54 ($CHCl_3$:MeOH = 9:1)

Example 190

Rf : 0.66 ($CHCl_3$:MeOH = 9:1)

Example 191

mp : 186-190°C
Rf : 0.611 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 192

mp : 194-197°C
Rf : 0.48 ($CHCl_3$:MeOH = 9:1)

Example 193

Rf : 0.39 ($CHCl_3$:MeOH = 9:1)

Example 194

Rf : 0.70 ($CHCl_3$:MeOH = 9:1)

Example 195

mp : 159-161°C
Rf : 0.53 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 196

mp : 116-120°C
Rf : 0.83 ($CHCl_3$:MeOH = 9:1)

Example 197

mp : 88-95°C
Rf : 0.64 ($CHCl_3$:MeOH = 9:1)

Example 198

mp : 143-149°C
Rf : 0.57 ($CHCl_3$:MeOH = 9:1)

Example 199

mp : 182-186°c
Rf : 0.58 ($CHCl_3$:MeOH = 9:1)

Example 200

mp : 155-160°C
Rf : 0.58 ($CHCl_3$:MeOH =9:1)

Example 201

mp : 180-181°C
Rf : 0.58 ($CHCl_3$:MeOH = 9:1)

Example 202

mp : 199-200°C
Rf : 0.38 ($CHCl_3$:MeOH = 9:1)

Reference Example 2

To a mixture of phenylacetyl chloride (0.27 g) and HCl·H-1-Leu-D-Trp(CHO)-βAla-OPac (0.94 g) in DMF (10 ml) was added triethylamine (0.54 ml) at 0°C. After 30 minutes, the solvent was evaporated in vacuo and the residue was dissolved in ethyl acetate (50 ml). The solution was washed with 0.5N hydrochloric acid (30 ml), dried over magnesium

sulfate and concentrated in vacuo. The residual solid was triturated with ethyl ether to give the object compound (0.93 g).

mp : 163-171°C

Rf : 0.45 (chloroform:methanol = 9:1)

The object compounds in Examples 203 to 211 could be obtained by reacting the corresponding starting compounds (I-a) and (IV) in a similar manner to that of Example 71 or Reference Example 2.

The physico-chemical properties of these object compounds are provided hereinbelow.

Example 203

mp : 168-170°C

Rf : 0.72 ($CHCl_3$:MeOH = 9:1)

Example 204

Rf : 0.47 ($CHCl_3$:MeOH = 9:1)

Example 205

mp : 198-199°C

Rf : 0.65 ($CHCl_3$:MeOH = 9:1)

Example 206

mp : 104-107°C

Rf : 0.59 ($CHCl_3$:MeOH = 9:1)

Example 207

mp : 228-230°C

Rf : 0.57 ($CHCl_3$:MeOH = 9:1)

Example 208

mp : 196-199°C

Rf : 0.53 ($CHCl_3$:MeOH = 9:1)

Example 209

mp : 207-212°C

Rf : 0.51 ($CHCl_3$:MeOH = 9:1)

Example 210

mp : 186-190°C

Rf : 0.49 ($CHCl_3$:MeOH = 9:1)

Example 211

Rf : 0.49 ($CHCl_3$:MeOH = 9:1)

The object compounds in Examples 212 to 216 could be obtained by reacting the corresponding starting compounds (V) and (VI) in a similar manner to that of Example 90.

The physico-chemical properties of these object compounds are provided hereinbelow.

Example 212

mp : 145-148°C

Rf : 0.68 ($CHCl_3$:MeOH = 9:1)

Example 213

mp : 120-130°C
Rf : 0.85 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 214

mp : 145-148°C
Rf : 0.88 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 215

mp : 165-167°C
Rf : 0.91 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 216

Rf : 0.37 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 217

Rf : 0.56 ($CHCl_3$:MeOH = 19:1)

Example 218

Rf : 0.45 ($CHCl_3$:MeOH = 19:1)

Example 219

Rf : 0.45 ($CHCl_3$:MeOH = 19:1)

Example 220

Rf : 0.71 ($CHCl_3$:MeOH = 9:1)

Example 221

mp : 120-130°C
Rf : 0.85 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 222

mp : 120-122°C
Rf : 0.72 ($CHCl_3$:MeOH = 9:1)

Example 223

To a solution of N-phenylacetyl-1-Leu-D-Trp(Me)-D-Lys(Z)-OBzl (0.10 g) in DMF (2 ml) were added 10%-palladium on activated carbon (30 mg) and ammonium formate (0.2 g) at room temperature. After 3 hours, the suspended mixture was filtered and the filtrate was evaporated in vacuo. The residue was dissolved in 1N hydrochloric acid (1 ml) and purified with "Diaion HP-20" (Trademark, made by Mitsubishi Chemical Industries) column chromatography (eluent: MeOH), and lyophilized to give the object compound (57.4 mg).

mp : 142-160°C
Rf : 0.26 (chloroform:methanol:28% aqueous ammonia = 5:3:1)
FAB-MS m/z : 578 [M+H]

Example 224

N-Phenylacetyl-1-His(Tos)-D-Trp(CHO)-βAla-OMe (0.32 g) and pyridine hydrochloride (0.6 g) were reacted in DMF (6 ml) in a similar manner to that of Example 171 to give the object compound (0.20 g).

mp : 160-166°C

Rf : 0.30 (10% MeOH in $CHCl_3$)

Example 225

Boc-D-allolle-1-Leu-D-Trp-D-Pya-OEt (2.0 g), and 4N HCl in dioxane (35 ml) were reacted in a similar manner to that of Preparation 1-2) to give the object compound (1.82 g).

Rf : 0.62 ($CHCl_3$:MeOH:AcOH = 8:2:1)

The object compounds in Examples 226 to 232 were obtained by reacting the corresponding Pac ester compounds (I-c), Zn powder, acetic acid and DMF in a similar manner to that of Reference Example 1.

The object compounds in Examples 233 to 234, 237 to 269, 272 to 280, 282-283, and 284 to 289 were obtained by reacting the corresponding methyl, ethyl, benzyl or Pac ester compound (I-c) with an aqueous NaOH in a similar manner to that of Example 1-2), 8 or 15.

The object compounds in Examples 235 to 236 and 270 to 271 were obtained by hydrogenating the corresponding benzyl, ester compound (I-c) in a similar manner to that of Preparation 1-4).

Example 281

N-(ε-Caprolactam-3-ylaminocarbonyl)-1-Leu-OH (293 mg), 2HCl·H-D-Trp(Me)-D-Pya-OEt (400 mg), WSCD (159 mg), HOBt (139 mg), Et_3N (87 mg) and DMF (10 ml) were reacted in a similar manner to that of Example 1-1) to give the object compound (411 mg).

The physico-chemical properties of these object compounds of Examples 269 to 355 are provided hereinbelow.

Example 226

mp : 150-153°C

Rf : 0.52 ($CHCl_3$:MeOH:AcOH = 16:1:1)

FAB-MS m/z : 719 [M+H]

Example 227

mp : 196-199°C

Rf : 0.52 ($CHCl_3$:MeOH:AcOH = 16:1:1)

FAB-MS m/z : 719 [M+H]

Example 228

mp : 90-100°C

Rf : 0.50 ($CHCl_3$:MeOH:AcOH = 16:1:1)

FAB-MS m/z : 649 [M+H]

Example 229

mp : 140-148°C

Rf : 0.50 ($CHCl_3$:MeOH:AcOH = 16:1:1)

FAB-MS m/z : 708 [M+H]

Example 230

mp : 95-105°C

Rf : 0.44 ($CHCl_3$:MeOH:AcOH = 16:1:1)

FAB-MS m/z : 670 [M+H]

Example 231

mp : 183-185°C
Rf : 0.36 ($CHCl_3$:MeOH:AcOH = 16:1:1)
FAB-MS m/z : 671 [M+H]

Example 232

Rf : 0.32 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 233

Rf : 0.32 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 234

Rf : 0.68 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 235

mp : 188-190°C
Rf : 0.31 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 236

mp : 202-205°C
Rf : 0.29 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 237

Rf : 0.10 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 238

Rf : 0.07 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 239

Rf : 0.10 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 240

Rf : 0.09 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 241

Rf : 0.11 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 242

Rf : 0.22 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Example 243

Rf : 0.29 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 244

Rf : 0.33 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 245

Rf : 0.45 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 246

Rf : 0.29 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 247

Rf : 0.33 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 248

Rf : 0.53 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 249

Rf : 0.28 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 250

Rf : 0.25 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 251

Rf : 0.62 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 252

Rf : 0.64 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 253

Rf : 0.46 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 254

mp : 248°C (dec.)
Rf : 0.27 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 255

Rf : 0.32 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 256

mp : 142-147°C
Rf : 0.34 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 257

Rf : 0.31 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 258

Rf : 0.37 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 259

Rf : 0.37 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 260

Rf : 0.20 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 261

Rf : 0.32 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 262

Rf : 0.36 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 263

Rf : 0.36 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 264

Rf : 0.36 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 265

Rf : 0.54 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 266

Rf : 0.54 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 267

Rf : 0.53 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 268

Rf : 0.53 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 269

Rf : 0.53 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 270

mp : 205-208°C
Rf : 0.27 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 271

mp : 200-210°C
Rf : 0.34 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 272

Rf : 0.61 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Example 273

mp : 103-110°C
Rf : 0.46 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Example 274

mp : 105-115°C
Rf : 0.48 ($CHCl_3$:MeOH:AcOH = 16:1:1)

Example 275

mp : 133-136°C
Rf : 0.47 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 276

mp : 158-162°C
Rf : 0.42 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 277

Rf : 0.64 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 278

Rf : 0.56 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 279

Rf : 0.30 ($CHCl_3$:MeOH = 9:1)

Example 280

Rf : 0.41 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 281

mp : 210-212°C
Rf : 0.44 ($CHCl_3$:MeOH = 9:1)

Example 282

Rf : 0.50 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 283

mp : 129-135°C
Rf : 0.37 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 284

mp : 162-167°C
Rf : 0.12 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 285

mp : 133-140°C
Rf : 0.52 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 286

mp : 208-210°C
Rf : 0.72 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 287

mp : 113-123°C
Rf : 0.72 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 288

mp : 160-164°C
Rf : 0.80 ($CHCl_3$:MeOH:AcOH = 8:1:1)

Example 289

Rf : 0.30 ($CHCl_3$:MeOH:AcOH = 8:1:1)

The object compounds in Examples 290 to 308, 310 to 311, 314 to 316, 318 to 326 and 334 could be obtained by reacting the corresponding carboxylic acid compounds (I-i) with substituted amines in a similar manner to that of Example 1-1).

The object compounds in Examples 309, 312 to 313, and 327 to 333 could be obtained by reacting the corresponding carboxylic acid or its ethyl ester compounds (I-i) with optionally substituted amines in a similar manner to that of Example 317.

Example 317

N-(Hexahydro-1H-azepin-1-ylcarbonyl)-1-Leu-D-Trp(Me)-D-Pya-OEt (0.20 g) was dissolved in 2.4N ammonia in methanol (10 ml) and the mixture was allowed to stand for 3 days at room temperature. Then the mixture was concentrated in vacuo and the residue was triturated with diethyl ether (10 ml) to give the object compound (0.18 g).

Example 335

N-(Hexahydro-1H-azepin-1-ylcarbonyl)-1-Leu-D-Trp(Me)-D-Pya-2-[(5S)-5-ethoxycarbonyl-2-oxopyrrolidin-1-yl] ethylamide (70 mg) and 2.4N NH_3 in MeOH (5 ml) were reacted in a similar manner to that of Example 383 to give the object compound (42.7 mg).

The physico-chemical properties of the object compounds of Examples 290 to 335 are provided hereinbelow.

Example 290

mp : 220-224°C
RF : 0.47 ($CHCl_3$:MeOH = 9:1)

Example 291

mp : 196-203°C
Rf : 0.36 ($CHCl_3$:MeOH = 9:1)

Example 292

Rf : 0.62 ($CHCl_3$:MeOH = 9:1)

Example 293

mp : 140-145°C
Rf : 0.52 ($CHCl_3$:MeOH = 9:1)

Example 294

Rf : 0.56 ($CHCl_3$:MeOH = 9:1)

Example 295

Rf : 0.60 ($CHCl_3$:MeOH = 9:1)

Example 296

Rf : 0.60 ($CHCl_3$:MeOH = 9:1)

Example 297

Rf : 0.58 ($CHCl_3$:MeOH = 9:1)

Example 298

Rf : 0.58 ($CHCl_3$:MeOH = 9:1)

Example 299

Rf : 0.53 ($CHCl_3$:MeOH = 9:1)

Example 300

Rf : 0.53 ($CHCl_3$:MeOH = 9:1)

Example 301

Rf : 0.52 ($CHCl_3$:MeOH = 9:1)

Example 302

Rf : 0.83 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 303

Rf : 0.83 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 304

Rf : 0.83 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 305

Rf : 0.83 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 306

Rf : 0.83 ($CHCl_3$:MeOH:AcOH = 8:2:1)

Example 307

mp : 190-195°C
Rf : 0.72 ($CHCl_3$:MeOH = 9:1)

Example 308

mp : 195-197°C
Rf : 0.76 ($CHCl_3$:MeOH = 9:1)

Example 309

Rf : 0.41 ($CHCl_3$:MeOH= 9:1)

Example 310

Rf : 0.44 ($CHCl_3$:MeOH = 9:1)

Example 311

mp : 160-164°C
Rf : 0.49 ($CHCl_3$:MeOH = 9:1)

Example 312

Rf : 0.44 ($CHCl_3$:MeOH = 9:1)

Example 313

mp : 200-203°C
Rf : 0.51 ($CHCl_3$:MeOH = 9:1)

Example 314

mp : 76-78°C
Rf : 0.54 ($CHCl_3$:MeOH = 9:1)

Example 315

mp : 75-78°C
Rf : 0.49 ($CHCl_3$:MeOH = 9:1)

Example 316

Rf : 0.64 ($CHCl_3$:MeOH = 9:1)

Example 317

mp : 110-112°C
Rf : 0.50 ($CHCl_3$:MeOH = 9:1)

Example 318

mp : 140-145°C
Rf : 0.64 ($CHCl_3$:MeOH = 9:1)

Example 319

Rf : 0.65 ($CHCl_3$:MeOH = 9:1)

Example 320

Rf : 0.62 ($CHCl_3$:MeOH = 9:1)

Example 321

Rf : 0.62 ($CHCl_3$:MeOH = 9:1)

Example 322

Rf : 0.62 ($CHCl_3$:MeOH = 9:1)

Example 323

Rf : 0.65 ($CHCl_3$:MeOH = 9:1)

Example 324

Rf : 0.45 ($CHCl_3$:MeOH = 9:1)

Example 325

mp : 165-167°C
Rf : 0.48 ($CHCl_3$:MeOH = 9:1)

Example 326

mp : 142-143°C
Rf : 0.50 ($CHCl_3$:MeOH = 9:1)

Example 327

mp : 168°C
Rf : 0.46 ($CHCl_3$:MeOH = 9:1)

Example 328

mp : 120-125°C
Rf : 0.47 ($CHCl_3$:MeOH = 9:1)

Example 329

mp : 115-125°C
Rf : 0,47 ($CHCl_3$:MeOH = 9:1)

Example 330

mp : 168°C
Rf : 0.41 ($CHCl_3$:MeOH = 9:1)

Example 331

mp : 215°C
Rf : 0.35 ($CHCl_3$:MeOH = 9:1)

Example 332

mp : 108-109°C
Rf : 0.34 ($CHCl_3$:MeOH = 19:1)

Example 333

mp : 119-120°C
Rf : 0.28 ($CHCl_3$:MeOH = 19:1)

Example 334

Rf : 0.49 ($CHCl_3$:MeOH = 9:1)

Example 335

mp : 195-197°C
Rf : 0.26 ($CHCl_3$:MeOH = 9:1)

Example 336

N-(Hexahydro-1H-azepin-1-ylcarbonyl)-1-Leu-D-Trp(Me)-OH (400 Ing), N-(ethoxycarbonylmethyl)-N-(pyridin-2-ylmethyl)amine (187 mg), HOBT (131 mg), WSLD-HCl (150 mg) and DMF (5 ml) were reacted in a similar manner to that of Example 1-1) to give the object compound (554 mg).
Rf : 0.37 ($CHCl_3$:MeOH = 20:1)

Example 337

N-(Hexahydro-1H-azepin-1-ylcarbonyl)-1-Leu-D-Trp(Me)-OH (400 mg), N-(ethoxycarbonylmethyl)-N-[2-(pyridin-2-yl)ethyl]amine dihydrochloride (271 mg), HOBT (131 mg), WSCD (150 mg), N-methylmorpholine (98 mg) and DMF (5 ml) were reacted in substantially the same manner to that of Example 90 to give the object compound (288 mg).
Rf : 0.32 ($CHCl_3$:MeOH = 20:1)

Example 338

Cyclohexyl isocyanate (60 mg), 2HCl·H-D-allolle-L-Leu-D-Trp(Me)-D-Pya-OEt (300 mg), Et_3N (87 mg) and DMF (10 ml) were reacted in a similar manner to that of Example 4-1) to give the object compound (260 mg).
mp : 235-237°C
Rf : 0.45 ($CHCl_3$:MeOH = 9:1)

Example 339

The object compound was obtained in 90.8% yield in substantially the same manner as that of Example 340.
mp : 111-115°C
Rf : 0.46 ($CHCl_3$:MeOH = 9:1)

Example 340

Boc-1-Leu-D-Trp(CH3)-D-Pya-OC_2H_5 (1.70 g) in TFA (20 ml) and anisole (2 ml) was reacted at 0°C for 1 hour and then the product was reacted with 4N HCl in 1,4-dioxane in a similar manner to that of Preparation 1-2) to give the object compound (1.60 g).
mp : 141-145°C
Rf : ($CHCl_3$:MeOH = 9:1)

The object compounds in Examples 341 to 345 could be obtained by removing t-butoxycarbonyl groups from the corresponding starting compounds (I-b) with TFA and anisole in a similar manner to that of Preparation 1-2).

The physico-chemical properties of these object compounds are provided hereinbelow.

Example 341

mp : 152-165°C
Rf : 0.32 ($CHCl_3$:MeOH = 9:1)

Example 342

Rf : 0.27 ($CHCl_3$:MeOH = 9:1)

Example 343

Rf : 0.26 ($CHCl_3$:MeOH = 9:1)

Example 344

mp : 194-202°C
Rf : 0.26 ($CHCl_3$:MeOH = 9:1)

Example 345

Rf : 0.26 ($CHCl_3$:MeOH = 9:1)

The object compounds in Examples 346 to 354 could be obtained by reacting the corresponding starting compounds with 4N hydrogen chloride in ethyl acetate in a similar manner to that of Example 21.

The physico-chemical properties of these object compounds are provided hereinbelow.

Example 346

mp : 103-120°C

Example 347

Rf : 0.41 ($CHCl_3$:MeOH = 9:1)

Example 348

Rf : 0.44 ($CHCl_3$MeOH = 9:1)

Example 349

Rf : 0.49 ($CHCl_3$MeOH = 9:1)

Example 350

Rf : 0.44 ($CHCl_3$MeOH = 9:1)

Example 351

Rf : 0.51 ($CHCl_3$:MeOH = 9:1)

Example 352

Rf : 0.65 ($CHCl_3$:MeOH = 9:1)

Example 353

mp : 110-135°C
Rf : 0.50 ($CHCl_3$:MeOH = 9:1)

Example 354

mp : 105-145°C
Rf : 0.49 ($CHCl_3$:MeOH = 9:1)

The compounds of Examples 355 to 357 could be obtained by reacting the corresponding starting compounds (II) and (III) in a similar manner to that of Example 1-1).

The physicochemical properties of these object compounds are provided hereinbelow.

Example 355

Rf : 0.44 ($CHCl_3$:MeOH = 9:1)

Example 356

Rf : 0.44 ($CHCl_3$:MeOH = 9:1)

Example 357

mp : 110-112°C
Rf : 0.50 ($CHCl_3$:MeOH = 9:1)

The compounds of Examples 358 to 360 could be obtained by reacting the corresponding starting compounds (V) and (VI) in a similar manner to that of Example 90.

The physicochemical properties of these object compounds are provided hereinbelow.

Example 358

Rf : 0.44 ($CHCl_3$:MeOH = 9:1)

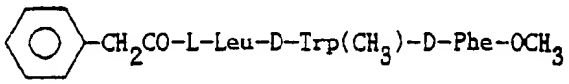
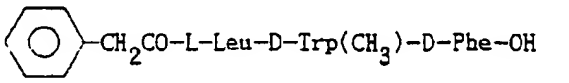
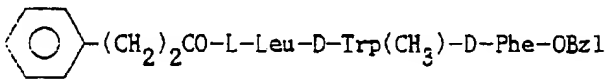
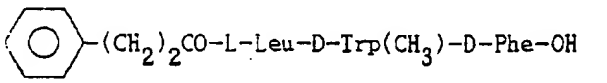
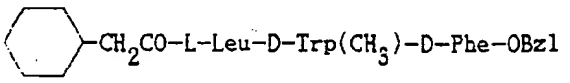
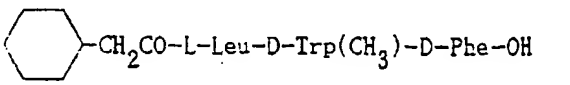
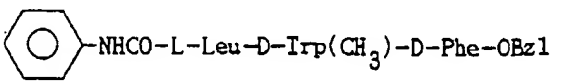
Examples 359

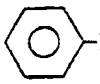
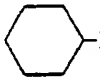
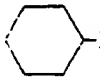
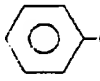
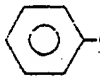
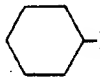
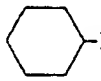
Rf : 0.44 ($CHCl_3$:MeOH = 9:1)

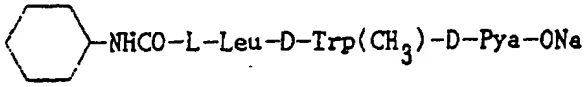
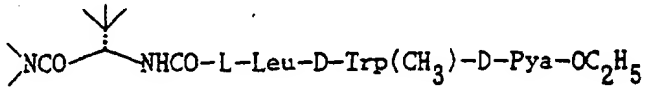
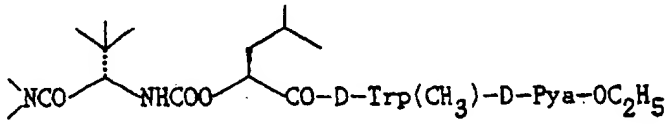
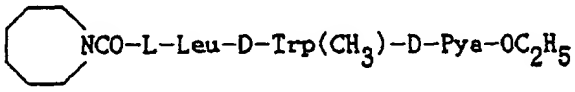
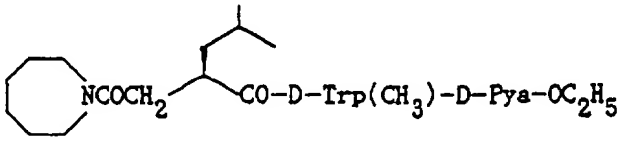
Example 360

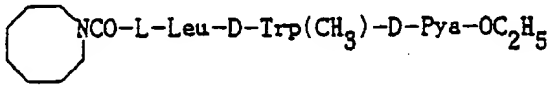
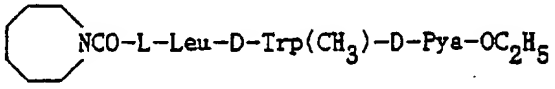
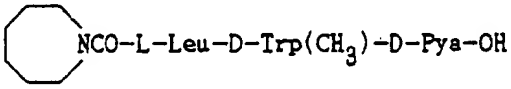
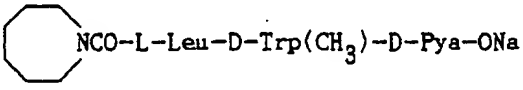
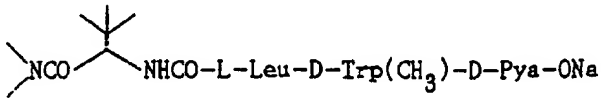
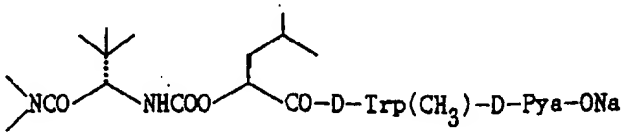
mp : 110-112°C
Rf : 0.50 ($CHCl_3$:MeOH = 9:1)

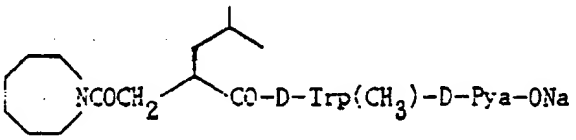
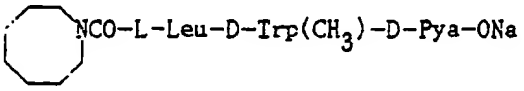
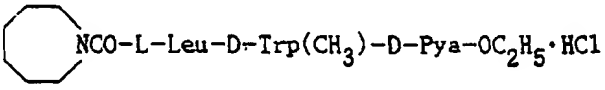
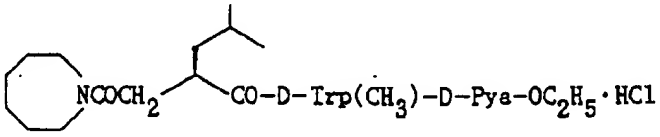
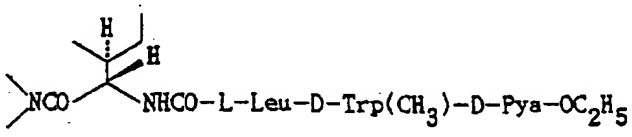
The object compounds obtained in the above Examples are given in the following Table.

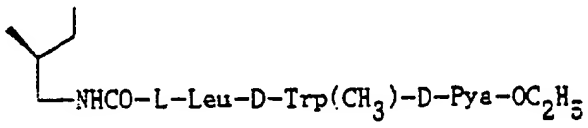
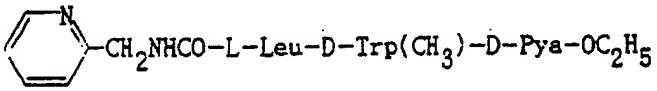
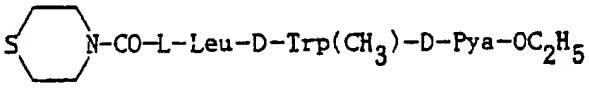
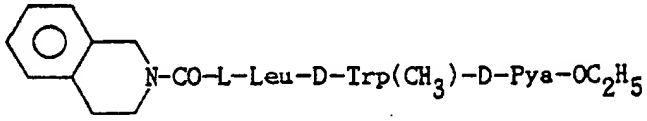
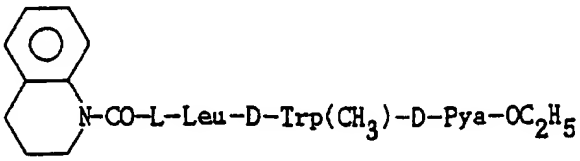
Example Nos.	Chemical Formulae
1 - 1)	
2)	
2 - 1)	
2)	
3 - 1)	
2)	
4 - 1)	

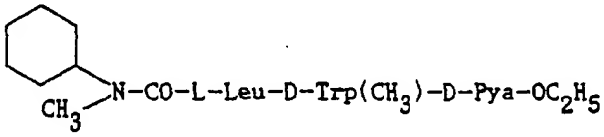
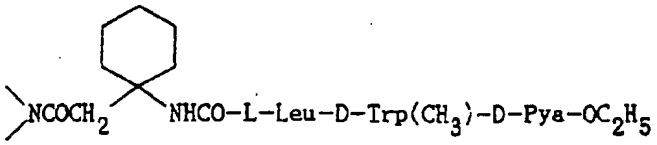
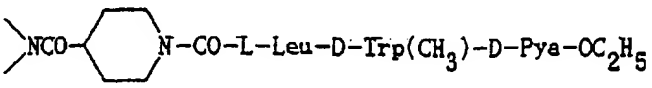
Example Nos.	Chemical Formulae
4 - 2)	 -NHCO-L-Leu-D-Trp(CH_3)-D-Phe-OH
5 - 1)	 -NHCO-L-Leu-D-Trp(CH_3)-D-Phe-OBzl
2)	 -NHCO-L-Leu-D-Trp(CH_3)-D-Phe-OH
6 - 1)	 -CH_2CO-L-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5·HCl
2)	 -CH_2CO-L-Leu-D-Trp(CH_3)-D-Pya-OH·HCl
7 - 1)	 -NHCO-L-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5
2)	 -NHCO-L-Leu-D-Trp(CH_3)-D-Pya-OH·HCl

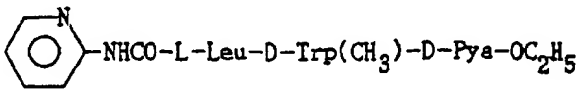
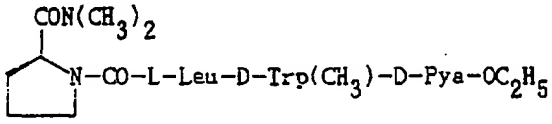
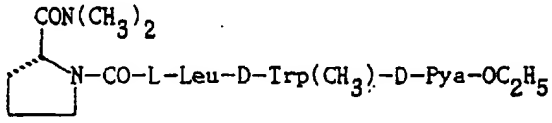
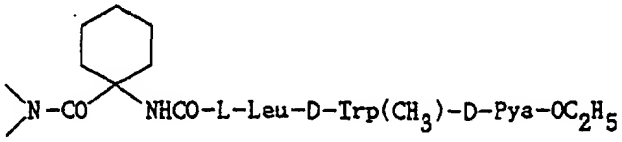
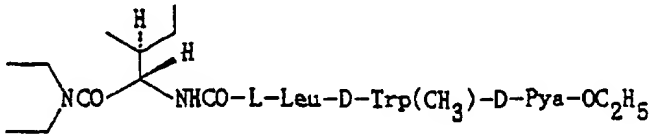
Example Nos.	Chemical Formulae
8	
9	
10	
11	
12	

Example Nos.	Chemical Formulae
13	
14	
15	
16	
17	
18	

Example Nos.	Chemical Formulae
19	
20	
21	
22	
23	

Example Nos.	Chemical Formulae
24	
25	
26	
27	
28	

Example Nos.	Chemical Formulae
29	$(n-C_4H_9)_2N-CO-L-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5$
30	$(n-C_3H_7)_2N-CO-L-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5$
31	$n-C_7H_{15}-NHCO-L-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5$
32	$(i-C_4H_9)_2N-CO-L-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5$
33	
34	
35	

Example Nos.	Chemical Formulae
36	
37	
38	
39	
40	

Example Nos.	Chemical Formulae
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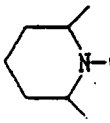
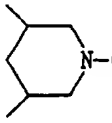
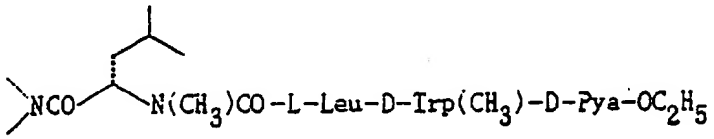
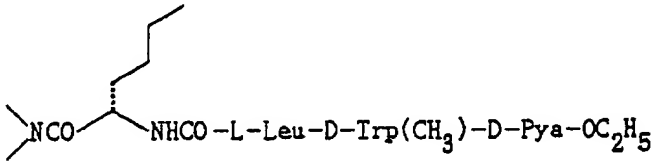
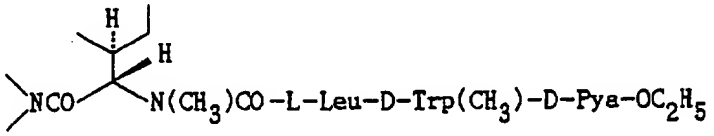
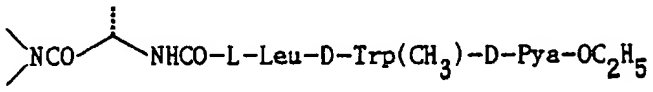
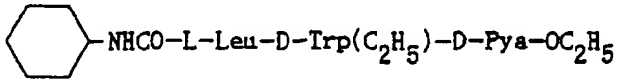
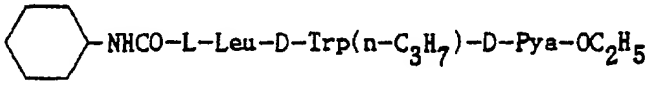
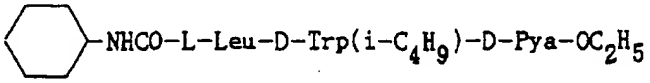
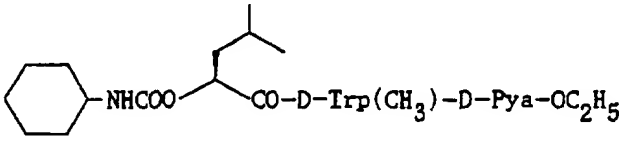
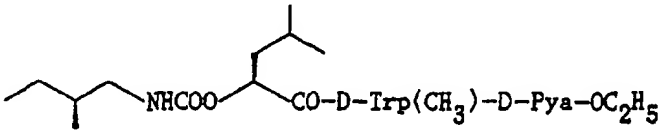
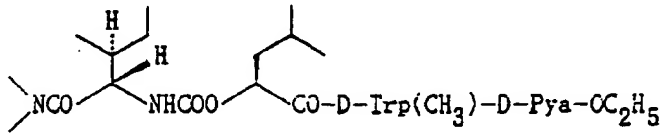
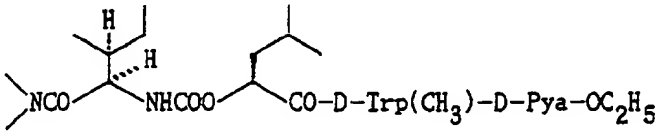
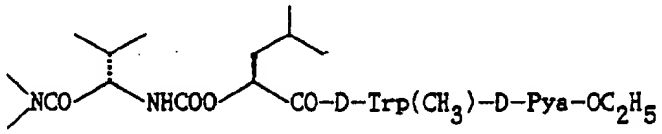
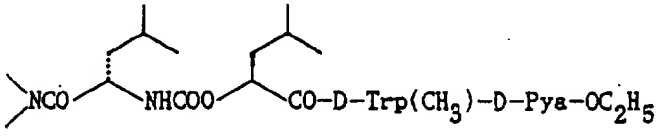
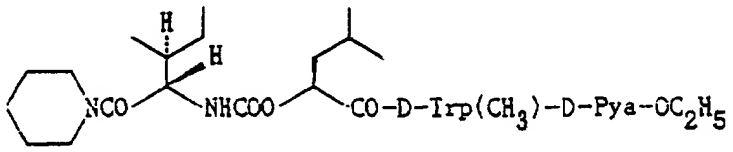
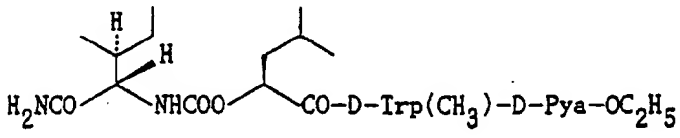
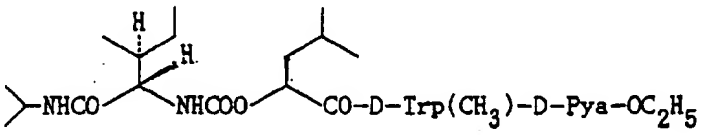
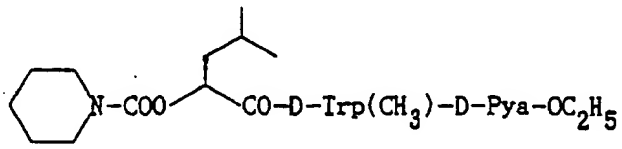
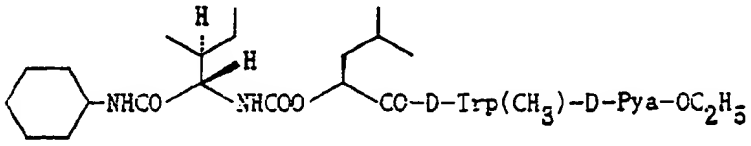
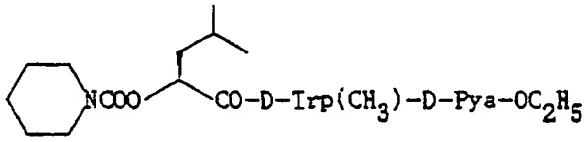
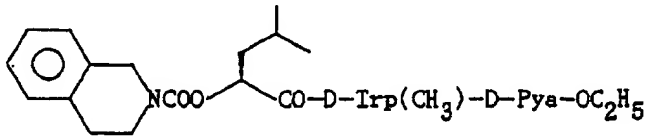
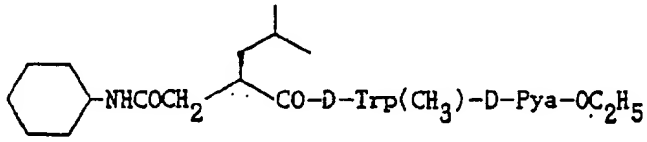
42	 N-CO-L-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5
43	 N-CO-L-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5
44	 $_2$NCO-L-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5
45	$(C_2H_5)_2$NCO-L-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5
46	$(i-C_3H_7)_2$NCO-L-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5

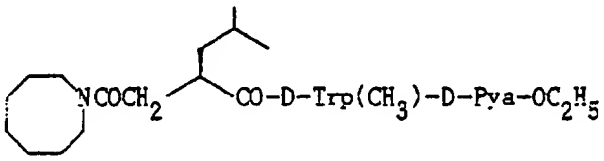
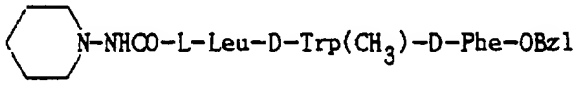
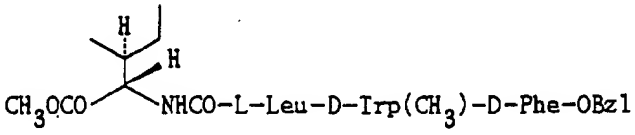
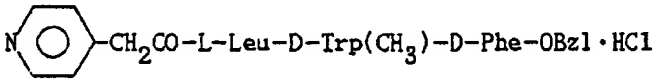
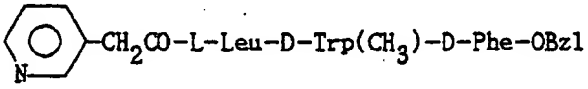
Example Nos.	Chemical Formulae
47	
48	
49	
50	

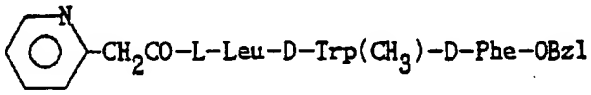
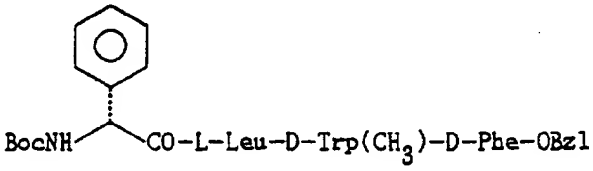
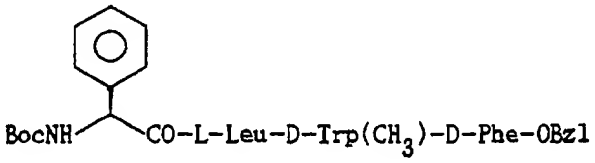
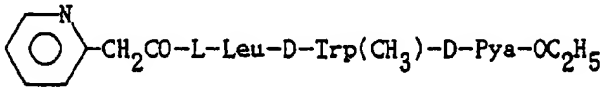
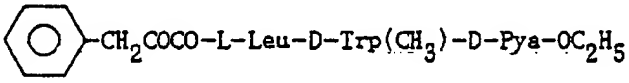
Example Nos.	Chemical Formulae
51	
52	
53	
54	
55	

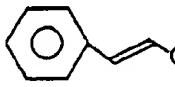
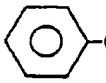
Example Nos.	Chemical Formulae
56	
57	
58	
59	

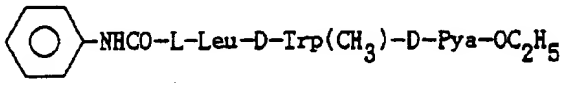
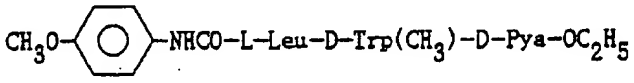
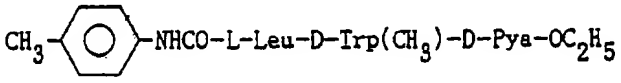
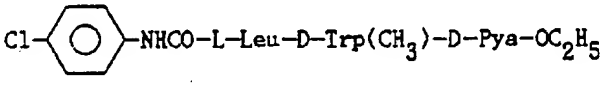
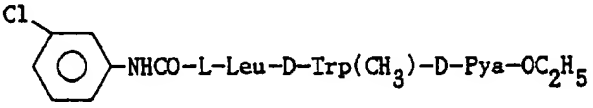
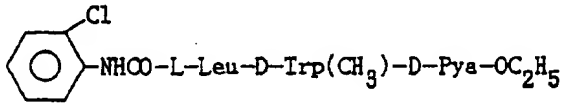
Example Nos.	Chemical Formulae
60	
61	
62	
63	

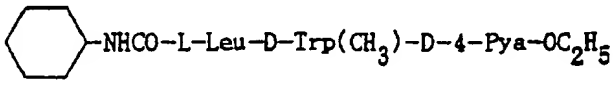
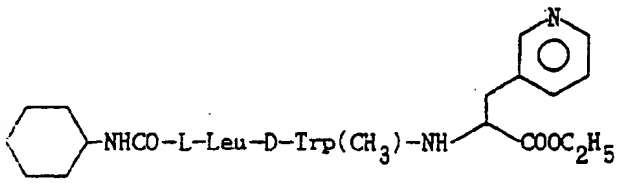
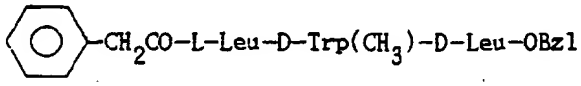
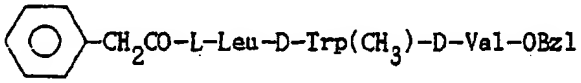
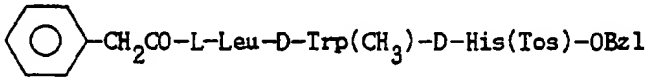
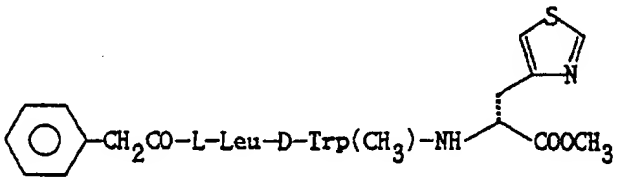
Example Nos.	Chemical Formulae
64	
65	
66	
67	

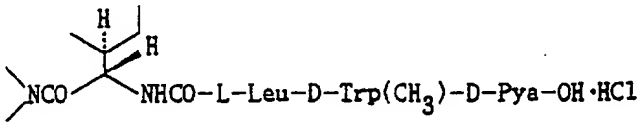
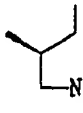
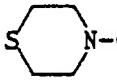
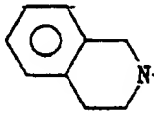
Example Nos.	Chemical Formulae
68	
69	
70	
71	
72	

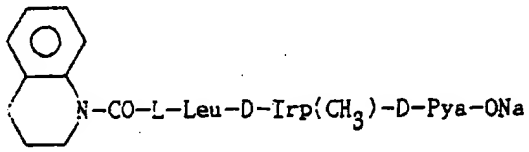
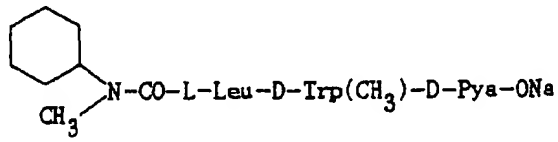
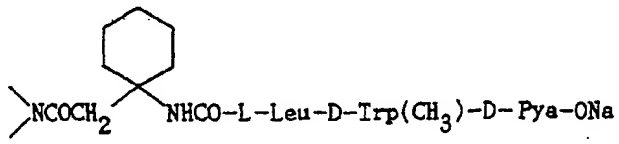
Example Nos.	Chemical Formulae
73	
74	
75	
76	
77	

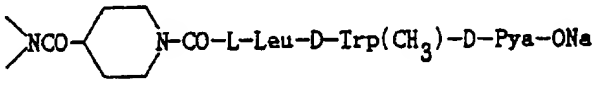
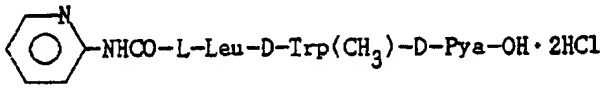
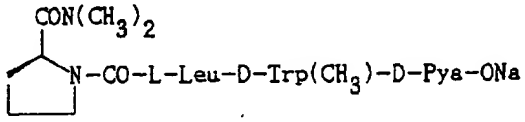
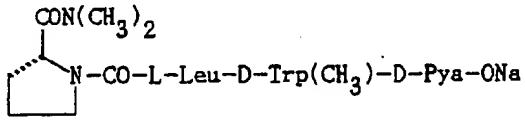
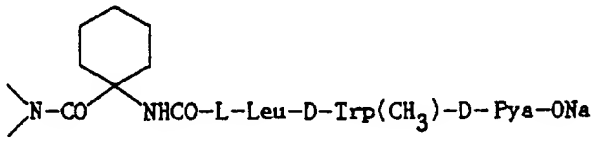
Example Nos.	Chemical Formulae
78	 CO-L-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5
79	 COCO-L-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5
80	 NCO-L-Leu-D-Trp(CH_3)-D-Pya-OEt·HCl
81	 CH_2SO_2-L-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5
82	 N-CO-L-Leu-D-Trp(CH_3)-D-Pya-OC_2H_5
83	 NHCO-L-Leu-D-Trp(CH_3)-D-Phe-OBzl

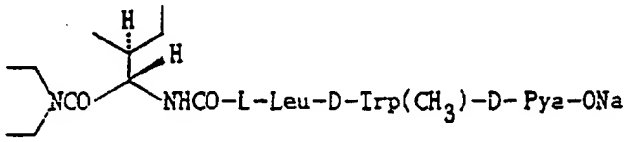
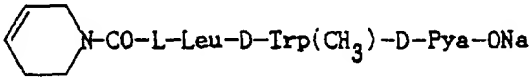
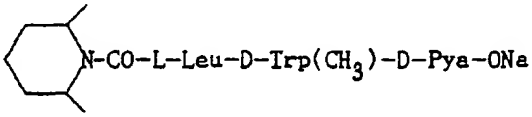
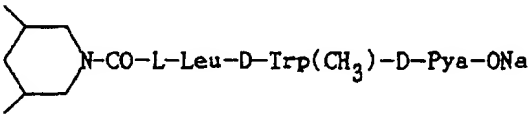
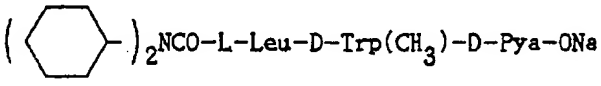
Example Nos.	Chemical Formulae
84	
85	
86	
87	
88	
89	

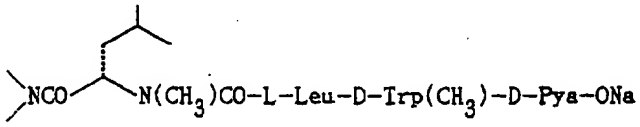
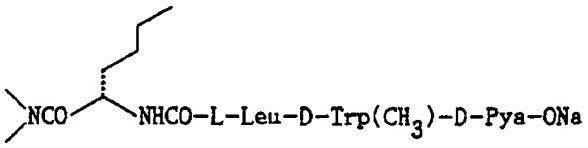
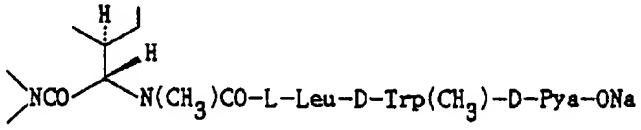
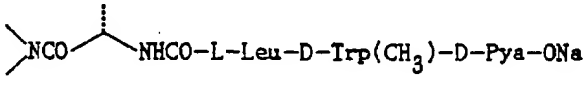
Example Nos.	Chemical Formulae
90	
91	
92	
93	
94	
95	

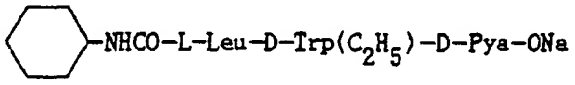
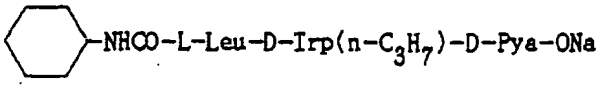
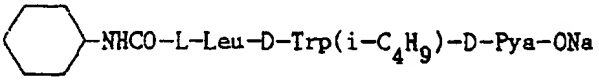
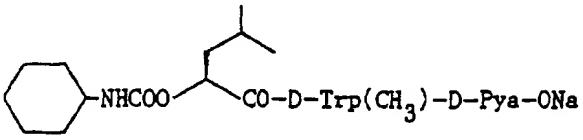
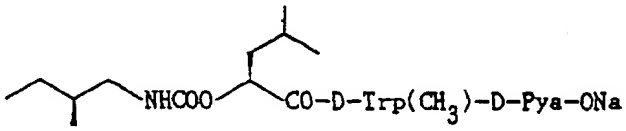
Example N.s.	Chemical Formulae
96	 NHCO-L-Leu-D-Trp(CH_3)-D-Pya-OH·HCl
97	 NHCO-L-Leu-D-Trp(CH_3)-D-Pya-OH·HCl
98	 CH_2NHCO-L-Leu-D-Trp(CH_3)-D-Pya-OH · 2HCl
99	 N-CO-L-Leu-D-Trp(CH_3)-D-Pya-ONa
100	 N-CO-L-Leu-D-Trp(CH_3)-D-Pya-ONa

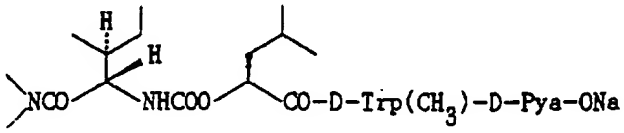
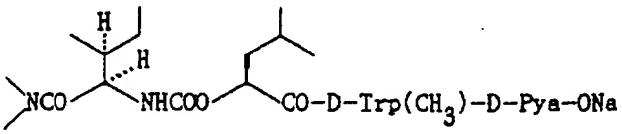
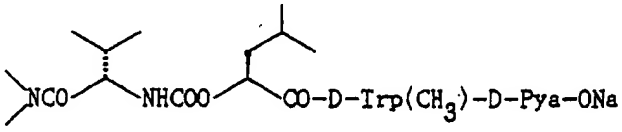
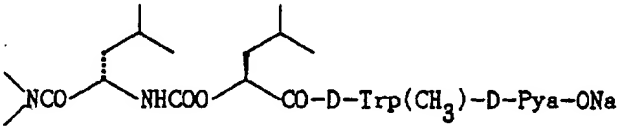
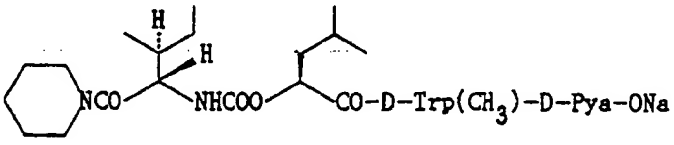
Example Nos.	Chemical Formulae
101	
102	$(n-C_4H_9)_2N-CO-L-Leu-D-Trp(CH_3)-D-Pya-ONa$
103	$(n-C_3H_7)_2N-CO-L-Leu-D-Trp(CH_3)-D-Pya-ONa$
104	$n-C_7H_{15}-NHCO-L-Leu-D-Trp(CH_3)-D-Pya-ONa$
105	$(i-C_4H_9)_2N-CO-L-Leu-D-Trp(CH_3)-D-Pya-ONa$
106	
107	

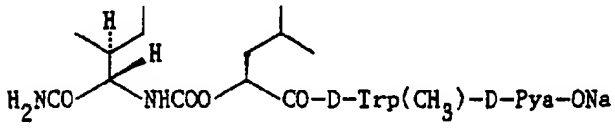
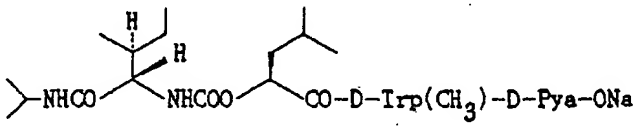
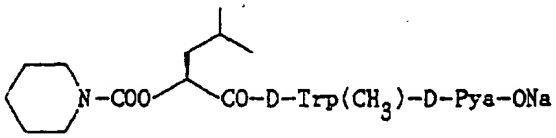
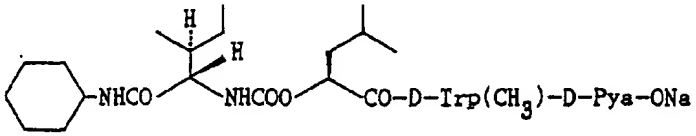
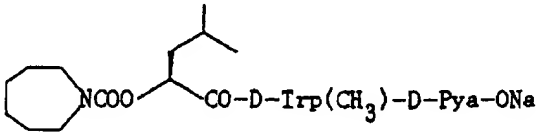
Example N s.	Chemical Formulae
108	
109	
110	
111	
112	

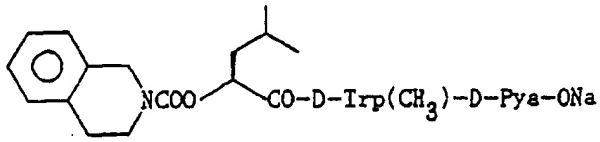
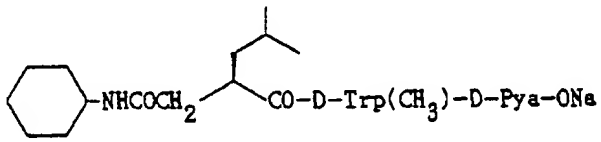
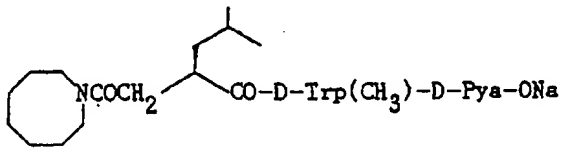
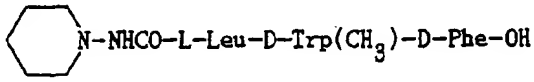
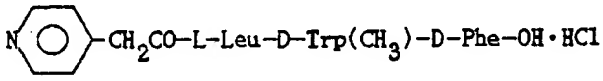
Example Nos.	Chemical Formulae
113	
114	
115	
116	
117	

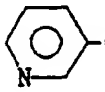
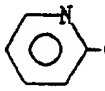
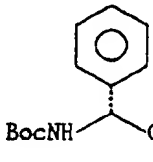
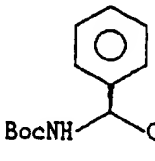
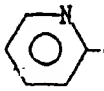
Example Nos.	Chemical Formulae
118	$(C_2H_5)_2NCO-L-Leu-D-Trp(CH_3)-D-Pya-ONa$
119	$(i-C_3H_7)_2NCO-L-Leu-D-Trp(CH_3)-D-Pya-ONa$
120	
121	
122	
123	

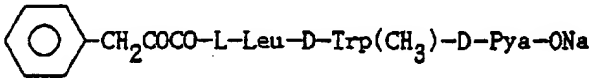
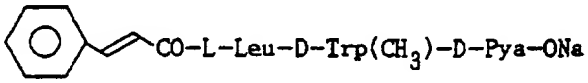
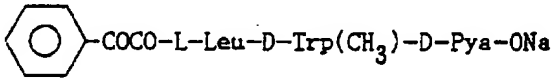
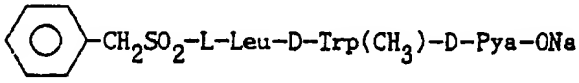
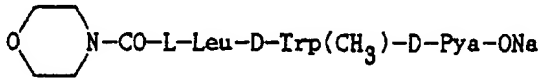
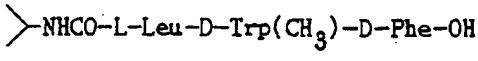
Example Nos.	Chemical Formulae
124	
125	
126	
127	
128	

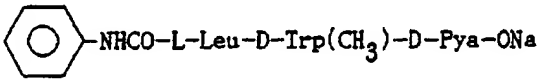
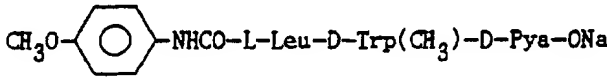
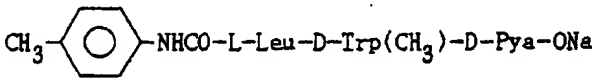
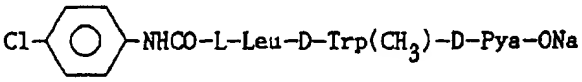
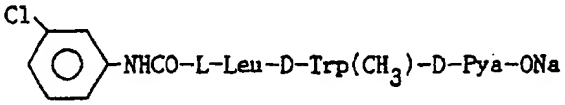
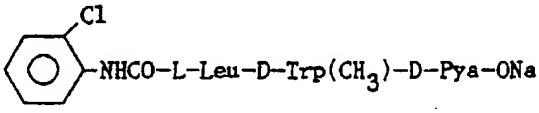
Example Nos.	Chemical Formulae
129	
130	
131	
132	
133	

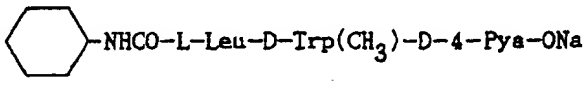
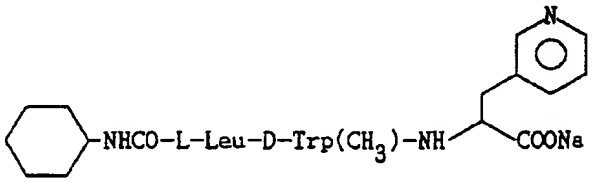
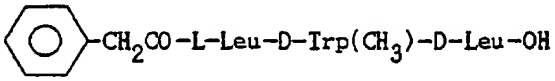
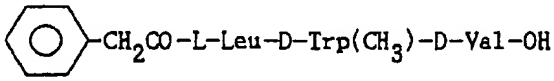
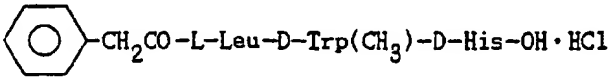
Example Nos.	Chemical Formulae
134	
135	
136	
137	
138	

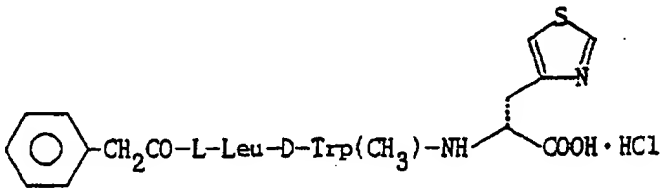
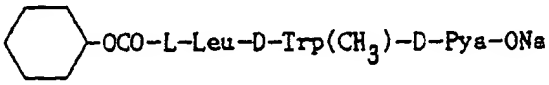
Example Nos.	Chemical Formulae
139	
140	
141	
142	
143	

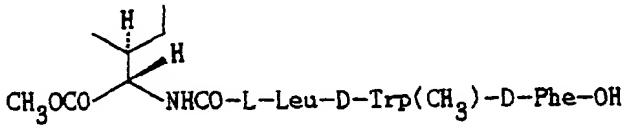
Example Nos.	Formulae
144	 $-CH_2CO-L-Leu-D-Trp(CH_3)-D-Phe-OH \cdot HCl$
145	 $-CH_2CO-L-Leu-D-Trp(CH_3)-D-Phe-OH \cdot HCl$
146	 $CO-L-Leu-D-Trp(CH_3)-D-Phe-OH$
147	 $CO-L-Leu-D-Trp(CH_3)-D-Phe-OH$
148	 $-CH_2CO-L-Leu-D-Trp(CH_3)-D-Pya-OH \cdot 2HCl$

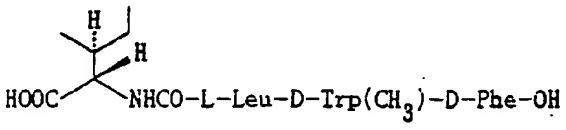
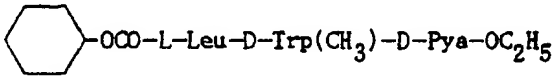
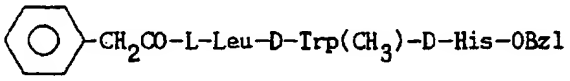
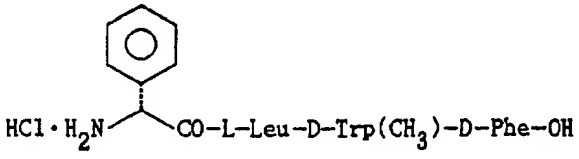
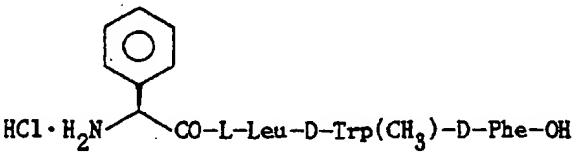
Example Nos.	Formulae
149	
150	
151	
152	
153	
154	

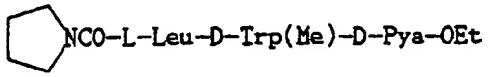
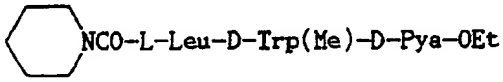
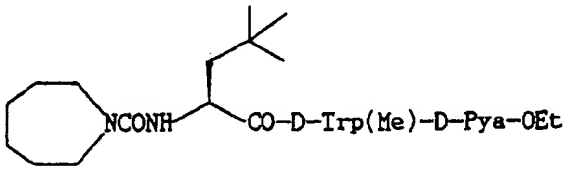
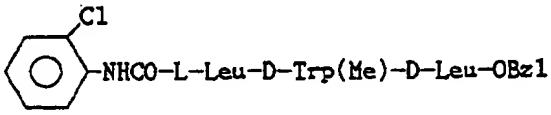
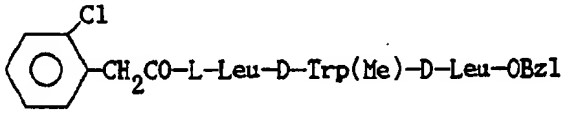
Example Nos.	Formulae
155	
156	
157	
158	
159	
160	

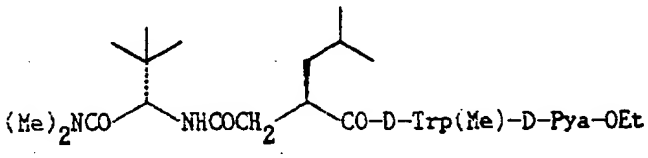
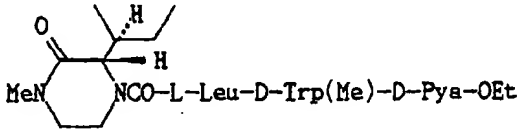
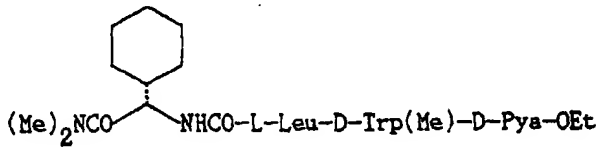
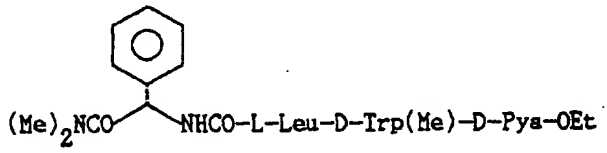
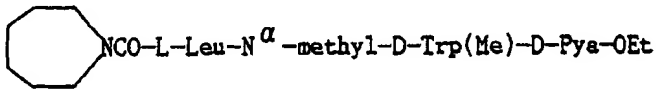
Example Nos.	Formulae
161	
162	
163	
164	
165	

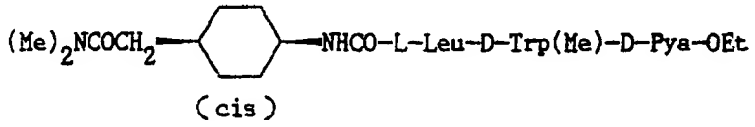
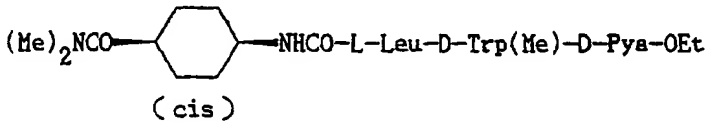
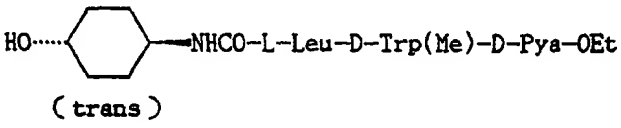
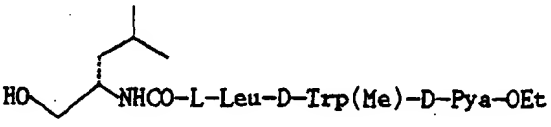
Example Nos.	Formulae
166	
167	

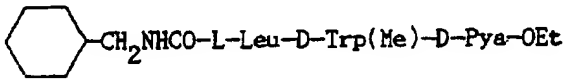
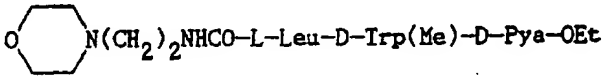
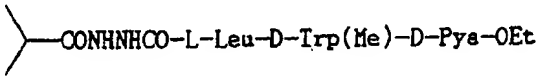
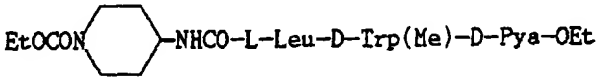
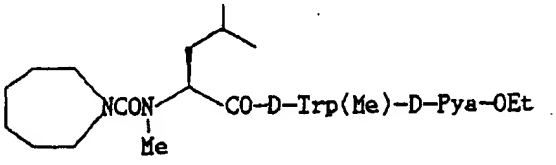
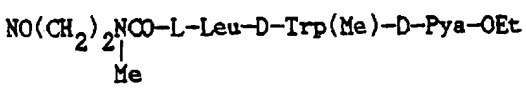
Example Nos.	Chemical Formulae
168	

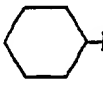
Example Nos.	Formulae
169	
170	
171	
172	
173	

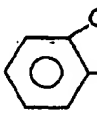
Example Nos.	Chemical Formulae
174	
175	
176	
177	
178	

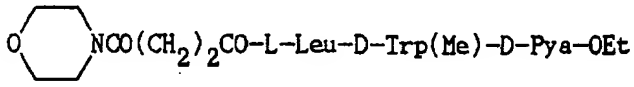
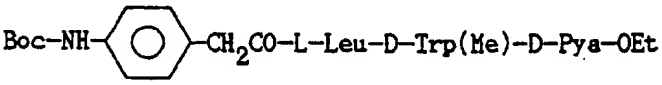
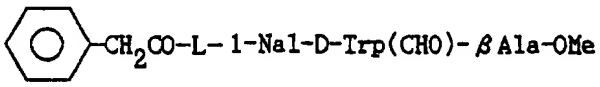
Example Nos.	Chemical Formulae
179	
180	
181	
182	
183	

Example Nos.	Chemical Formulae
184	 (cis)
185	 (cis)
186	$(Me)_2NCOCH_2NHCO-L-Leu-D-Trp(Me)-D-Pya-OEt$
187	$(Me)_2NCO(CH_2)_2NHCO-L-Leu-D-Trp(Me)-D-Pya-OEt$
188	 (trans)
189	

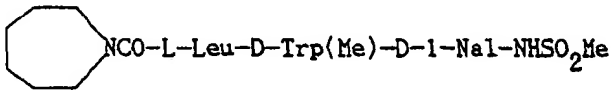
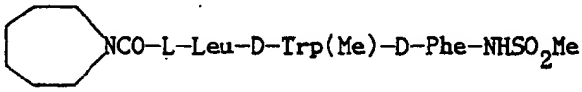
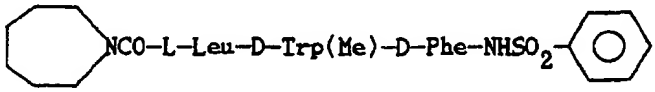
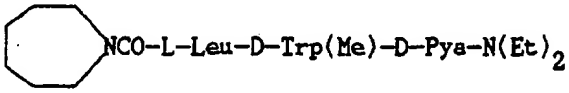
Example Nos.	Chemical Formul e
190	
191	
192	
193	
194	
195	

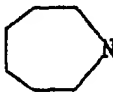
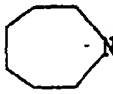
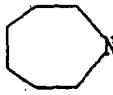
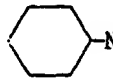
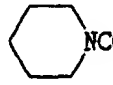
Example Nos.	Chemical Formulae
196	Boc－L－Leu－D－Trp(Me)－D－Phe－OBzl
197	Boc－L－His(Tos)－D－Trp(CHO)－βAla－OMe
198	Boc－L－Pya－D－Trp(CHO)－βAla－OMe
199	Boc－L－Phe－D－Trp(CHO)－βAla－OMe
200	Boc－L－Cha－D－Trp(CHO)－βAla－OMe
201	Boc－L－1－Nal－D－Trp(CHO)－βAla－OMe
202	 －NHCO－L－Leu－D－Phe－D－Pya－OEt

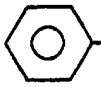
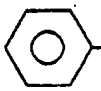
Example Nos.	Chemical Formulae
203	 －CH_2CO－L－Leu－D－Trp(Me)－D－Pya－OEt

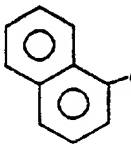
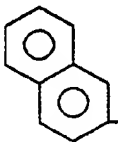
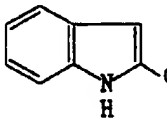
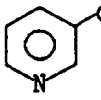
Example Nos.	Chemical Formulae
204	
205	Boc－D－alloIle－L－Leu－D－Trp(Me)－D－Pya－OEt
206	
207	

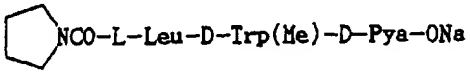
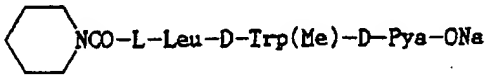
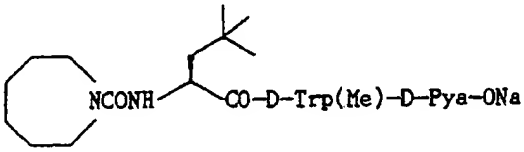
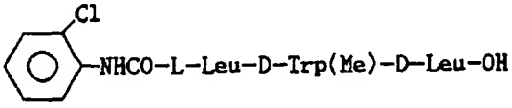
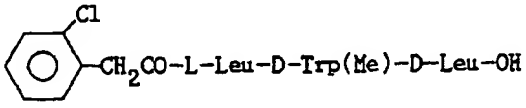
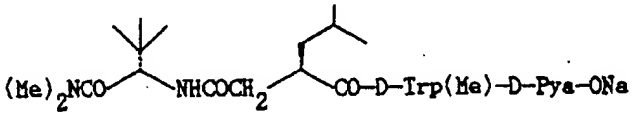
Example Nos.	Chemical Formulae
208	 CH_2CO-L-Cha-D-Trp(CHO)-βAla-OMe
209	 CH_2CO-L-Phe-D-Trp(CHO)-βAla-OMe
210	 CH_2CO-L-Pya-D-Trp(CHO)-βAla-OMe
211	 CH_2CO-L-His(Tos)-D-Trp(CHO)-βAla-OMe
212	 CH_2CO-L-Leu-D-Trp(Me)-D-Lys(Z)-OBzl

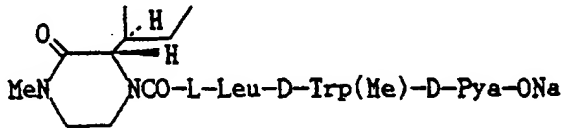
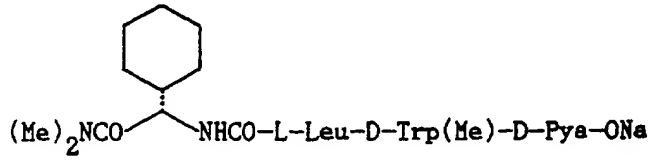
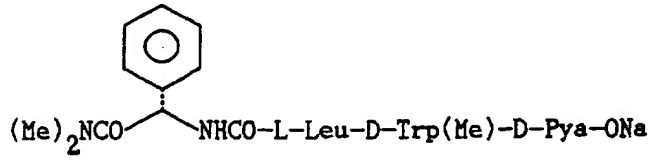
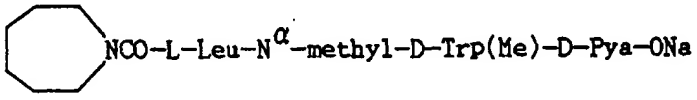
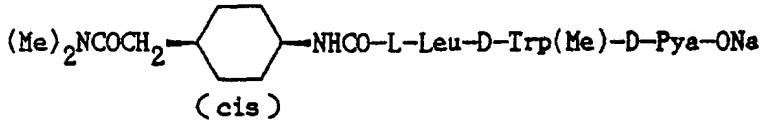
Example Nos.	Chemical Formulae
213	
214	
215	
216	

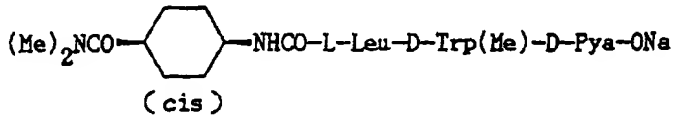
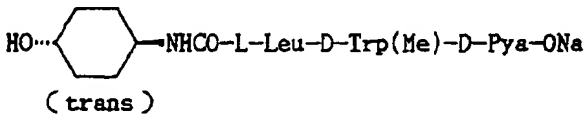
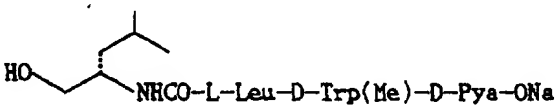
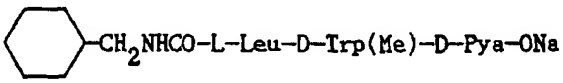
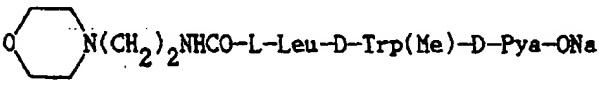
Example Nos.	Chemical Formulae
217	 NCO-L-Leu-D-Trp(Me)-D-1-Nal-OEt
218	 NCO-L-Leu-D-Trp(Me)-D-Phe-OEt
219	 NCO-L-Leu-D-Trp(Me)-D-Leu-OEt
220	 -NHCO-L-Leu-D-Trp(Me)-D-Leu-OBzl
221	 NCO-L-Leu-D-Trp(Me)-D-1-Nal-NHSO$_2$Me
222	Boc-L-Leu-D-Trp(Me)-D-Pya-OEt

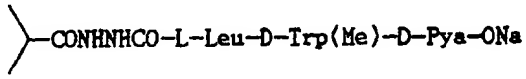
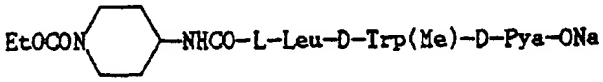
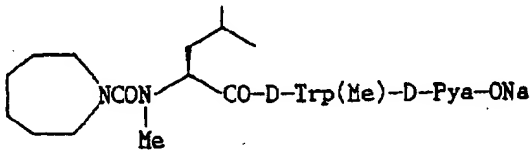
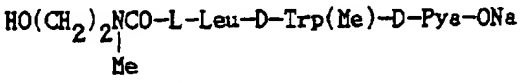
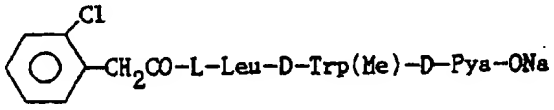
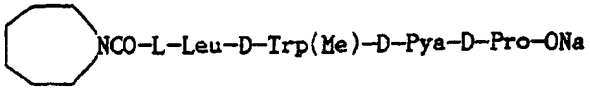
Example Nos.	Chemical Formulae
223	 CH_2CO-L-Leu-D-Trp(Me)-D-Lys-OH·HCl
224	 CH_2CO-L-His-D-Trp(CHO)-βAla-OMe
225	2HCl·H-D-alloIle-L-Leu-D-Trp(Me)-D-Pya-OEt

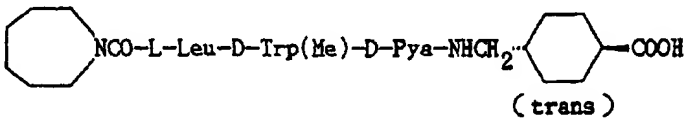
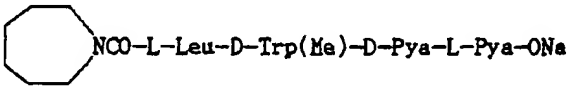
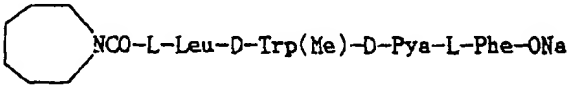
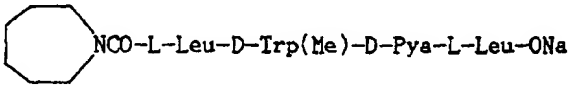
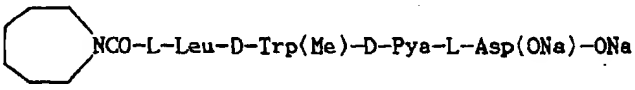
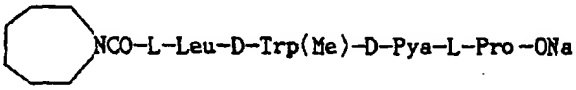
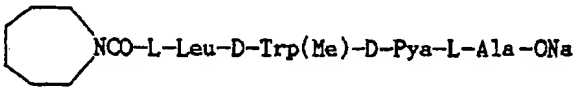
Example Nos.	Chemical Formulae
226	 CO-L-Leu-D-Trp(CHO)-D-Glu(OBzl)-OH
227	 CO-L-Leu-D-Trp(CHO)-D-Glu(OBzl)-OH
228	 CO-L-Leu-D-Trp(CHO)-D-Glu(OBzl)-OH
229	 CO-L-Leu-D-Trp(CHO)-D-Glu(OBzl)-OH
230	HCl·  CO-L-Leu-D-Trp(CHO)-D-Glu(OBzl)-OH
231	HCl·  CO-L-Leu-D-Trp(CHO)-D-Glu(OBzl)-OH

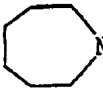
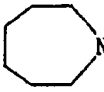
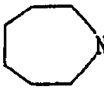
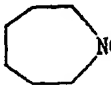
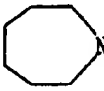
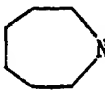
Example Nos.	Chemical Formulae
232	
233	
234	
235	
236	
237	

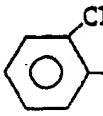
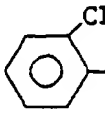
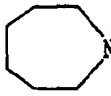
xample Nos.	Chemical Formulae
238	
239	
240	
241	
242	

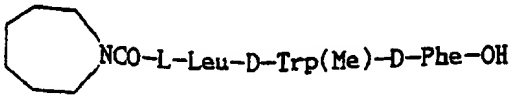
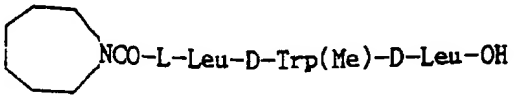
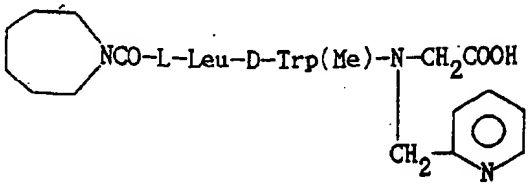
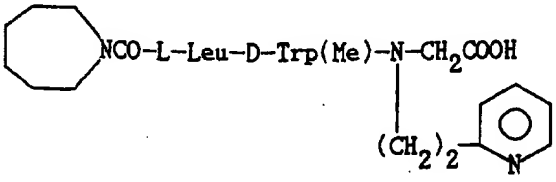
Example Nos.	Chemical Formulae
243	 (cis)
244	$(Me)_2NCOCH_2NHCO-L-Leu-D-Trp(Me)-D-Pya-ONa$
245	$(Me)_2NCO(CH_2)_2NHCO-L-Leu-D-Trp(Me)-D-Pya-ONa$
246	 (trans)
247	
248	
249	

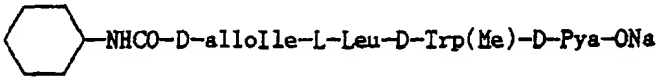
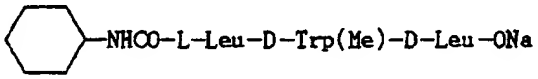
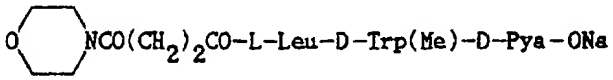
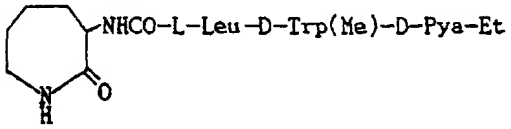
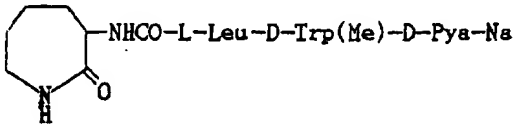
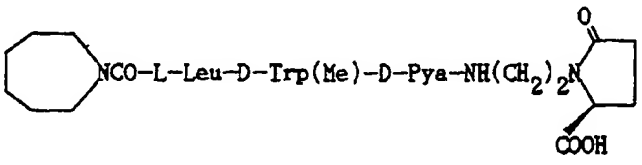
Example Nos.	Chemical Formulae
250	
251	
252	
253	
254	
255	

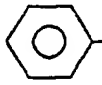
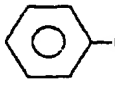
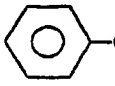
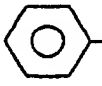
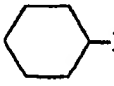
Example Nos.	Chemical Formulae
256	
257	
258	
259	
260	
261	
262	

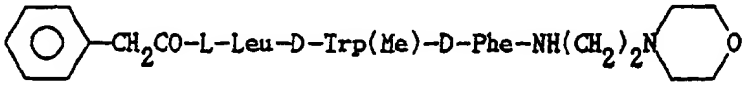
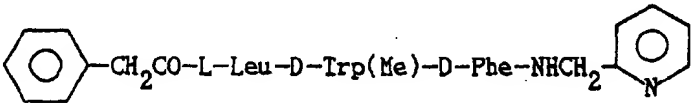
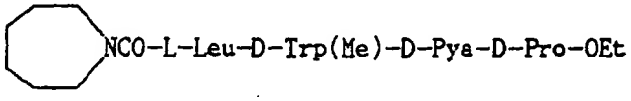
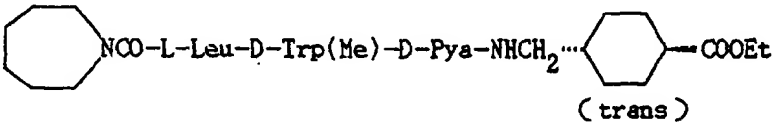
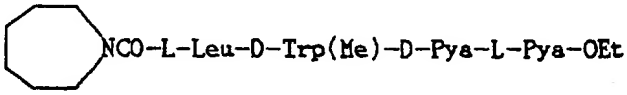
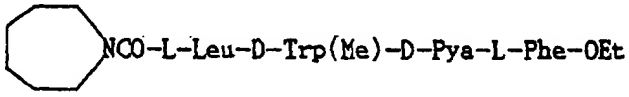
Example Nos.	Chemical Formulae
263	 NCO-L-Leu-D-Trp(Me)-D-Pya-L-Val-ONa
264	 NCO-L-Leu-D-Trp(Me)-D-Pya-Sar-ONa
265	 NCO-L-Leu-D-Trp(Me)-D-Pya-NH$(CH_2)_5$COONa
266	 NCO-L-Leu-D-Trp(Me)-D-Pya-NH$(CH_2)_4$COONa
267	 NCO-L-Leu-D-Trp(Me)-D-Pya-NH$(CH_2)_3$COONa
268	 NCO-L-Leu-D-Trp(Me)-D-Pya-βAla-ONa
269	 NCO-L-Leu-D-Trp(Me)-D-Pya-Gly-ONa

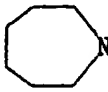
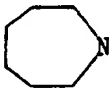
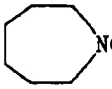
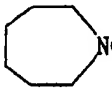
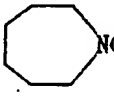
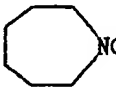
Example Nos.	Chemical Formulae
270	 -NHCO-L-Leu-D-Trp(Me)-D-Pya-βAla-OH
271	 -CH_2CO-L-Leu-D-Trp(Me)-D-Leu-βAla-OH
272	 NCO-L-Leu-D-Trp(Me)-D-1-Nal-OH

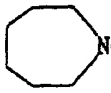
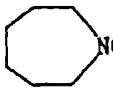
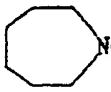
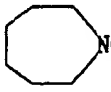
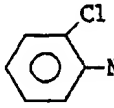
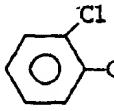
Example Nos.	Chemical Formulae
273	
274	
275	
276	
277	Boc－D－alloIle－L－Leu－D－Trp(Me)－D－Pya－ONa

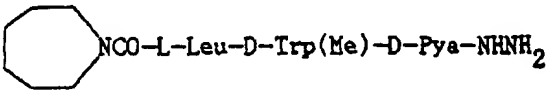
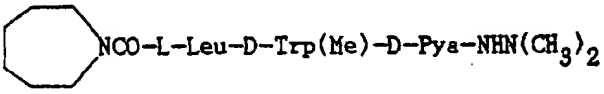
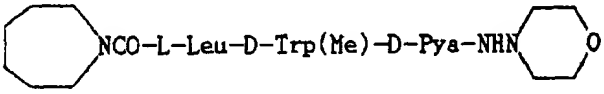
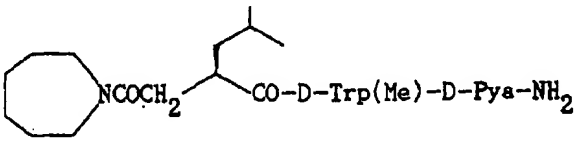
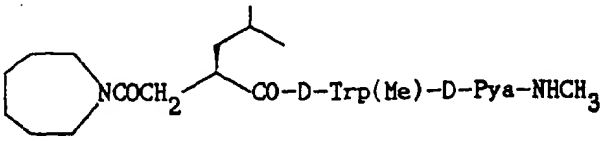
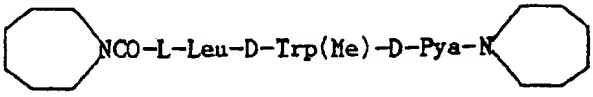
Example Nos.	Chemical Formulae
278	
279	
280	
281	
282	
283	

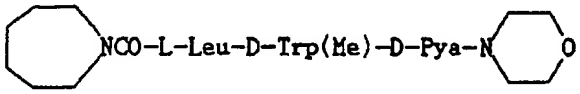
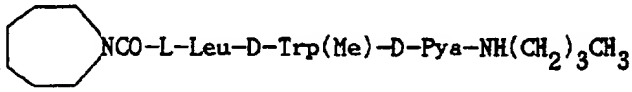
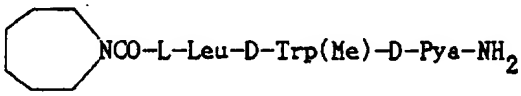
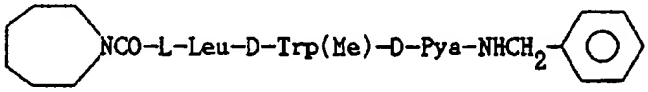
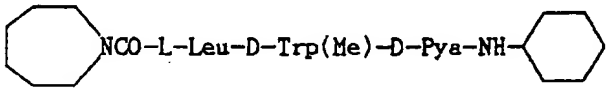
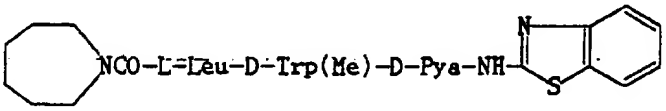
Example Nos.	Chemical Formulae
284	 $-CH_2CO-L-His-D-Trp-\beta Ala-OH$
285	 $-CH_2CO-L-Pya-D-Trp-\beta Ala-OH$
286	 $-CH_2CO-L-Phe-D-Trp-\beta Ala-OH$
287	 $-CH_2CO-L-Cha-D-Trp-\beta Ala-OH$
288	 $-CH_2CO-L-1-Nal-D-Trp-\beta Ala-OH$
289	 $-NHCO-L-Leu-D-Phe-D-Pya-ONa$

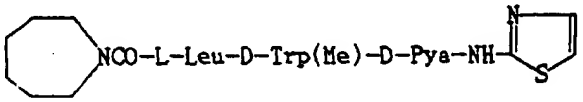
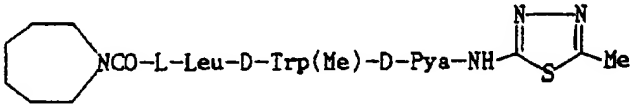
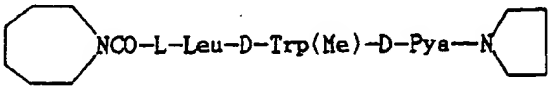
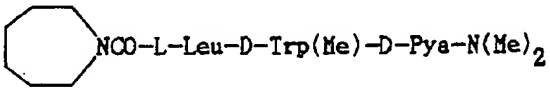
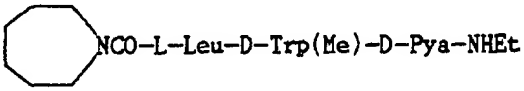
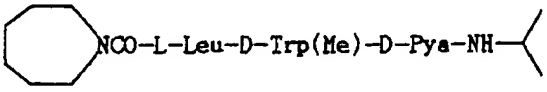
Example Nos.	Chemical Formulae
290	
291	
292	
293	
294	
295	

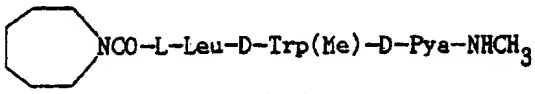
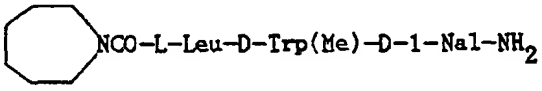
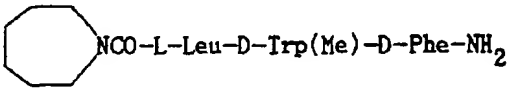
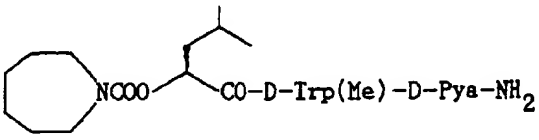
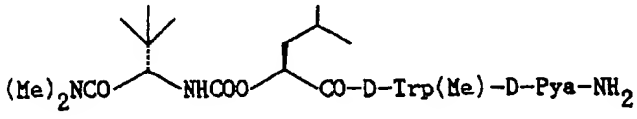
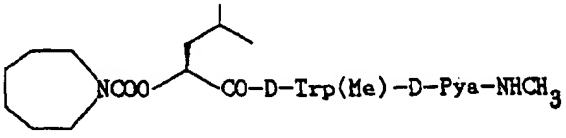
Example Nos.	Chemical Formulae
296	 NCO-L-Leu-D-Trp(Me)-D-Pya-L-Leu-OMe
297	 NCO-L-Leu-D-Trp(Me)-D-Pya-L-Asp(OMe)-OMe
298	 NCO-L-Leu-D-Trp(Me)-D-Pya-L-Pro-OMe
299	 NCO-L-Leu-D-Trp(Me)-D-Pya-L-Val-OMe
300	 NCO-L-Leu-D-Trp(Me)-D-Pya-Sar-OMe
301	 NCO-L-Leu-D-Trp(Me)-D-Pya-L-Ala-OPac
302	 NCO-L-Leu-D-Trp(Me)-D-Pya-NH(CH_2)$_5$COOPac

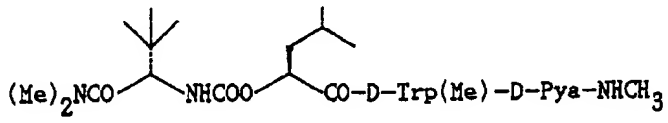
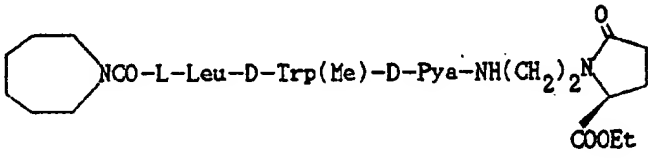
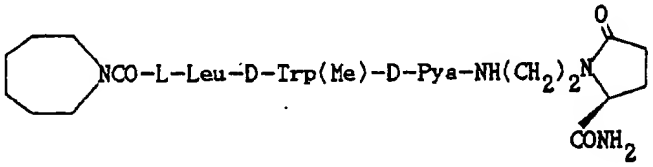
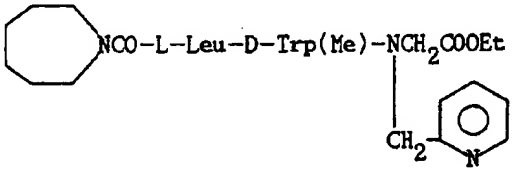
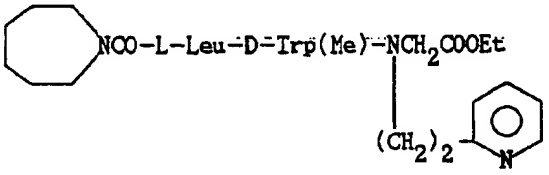
Example N s.	Chemical Formulae
303	 NCO-L-Leu-D-Trp(Me)-D-Pya-NH$(CH_2)_4$COOPac
304	 NCO-L-Leu-D-Trp(Me)-D-Pya-NH$(CH_2)_3$COOPac
305	 NCO-L-Leu-D-Trp(Me)-D-Pya-βAla-OBzl
306	 NCO-L-Leu-D-Trp(Me)-D-Pya-Gly-OMe
307	 NHCO-L-Leu-D-Trp(Me)-D-Pya-βAla-OBzl
308	 CH_2CO-L-Leu-D-Trp(Me)-D-Leu-βAla-OBzl

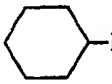
Example Nos.	Chemical Formulae
309	
310	
311	
312	
313	
314	

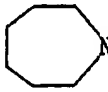
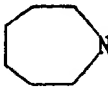
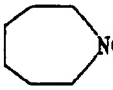
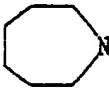
Example Nos.	Chemical Formulae
315	
316	
317	
318	
319	
320	

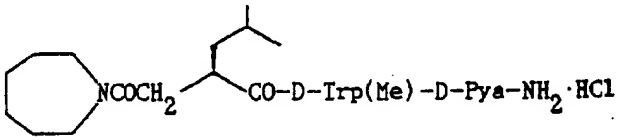
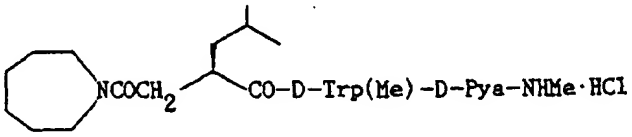
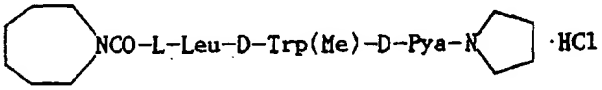
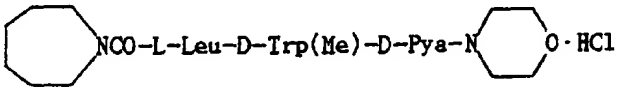
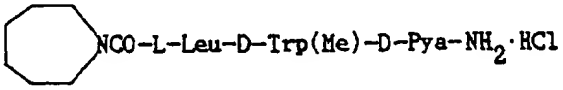
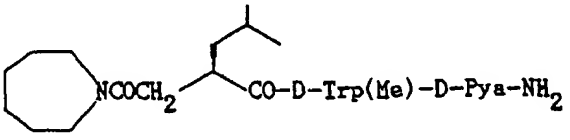
Example Nos.	Chemical Formulae
321	
322	
323	
324	
325	
326	

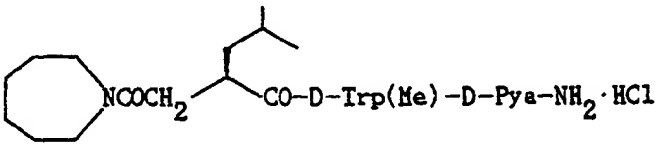
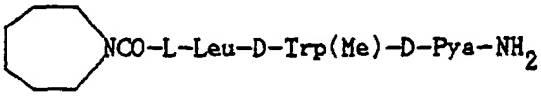
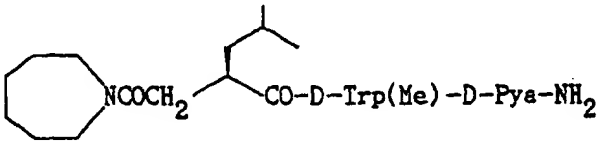
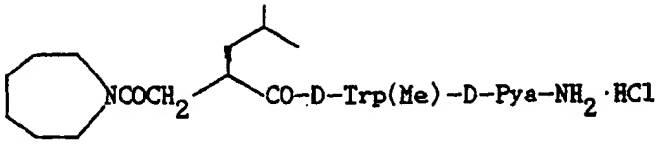
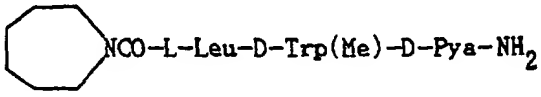
Example Nos.	Chemical Formulae
327	
328	
329	
330	
331	
332	

Example Nos.	Chemical Formulae
333	
334	
335	
336	
337	

Example Nos.	Chemical Formulae
338	 —NHCO–D–alloIle–L–Leu–D–Trp(Me)–D–Pya–OEt
339	HCl·H–L–Leu–D–Trp(Me)–D–Phe–OBzl
340	2HCl·H–L–Leu–D–Trp(Me)–D–Pya–OEt
341	HCl·H–L–1–Nal–D–Trp(CHO)–βAla–OMe
342	HCl·H–L–Cha–D–Trp(CHO)–βAla–OMe
343	HCl·H–L–Phe–D–Trp(CHO)–βAla–OMe
344	2HCl·H–L–Pya–D–Trp(CHO)–βAla–OMe

Example Nos.	Chemical Formulae
345	TFA·H−L−His(Tos)−D−Trp(CHO)−βAla−OMe
346	 NCO−L−Leu−D−Trp(Me)−D−Pya−$N(Me)_2$·HCl
347	 NCO−L−Leu−D−Trp(Me)−D−Pya−$NHNH_2$·2HCl
348	 NCO−L−Leu−D−Trp(Me)−D−Pya−$NHN(Me)_2$·2HCl
349	 NCO−L−Leu−D−Trp(Me)−D−Pya−NHN  ·2HCl

Example Nos.	Chemical Formulae
350	
351	
352	
353	
354	
355	

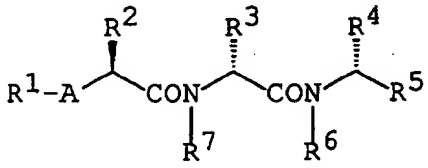
Exampl Nos.	Chemical Formulae
356	
357	
358	
359	
360	

In the above table, the configurations accompanied with cis or trans do not mean the absolute configurations,but the relative configurations only. The other configurations mean the absolute ones.

Claims

Claims for the following Contracting States : DE, AT, GB, FR, BE, IT, NL, CH, LI, LU, SE, DK

1. A peptide compound of the formula (I):



(I)

having endothelin receptor antagonistic activity,
in which

R^1 is hydrogen or acyl,

R^2 is C_1-C_6 alkyl;
C_6-C_{10} ar(C_1-C_6)alkyl optionally substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro and cyano; cyclo(C_1-C_6)alkyl(C_1-C_6)alkyl; or heterocyclic(C_1-C_6)alkyl optionally substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro, cyano and imino-protective group;
said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8 membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing a sulfur atom, or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

R^3 is heterocyclic(C_1-C_6)alkyl or
C_6-C_{10} ar(C_1-C_6)alkyl, each of which is optionally substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro, cyano and imino-protective group,
said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 8 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing a sulfur atom, or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

R^4 is C_1-C_6 alkyl, C_6-C_{10} ar(C_1-C_6)alkyl,
amino(C_1-C_6)alkyl,protected amino(C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl,protected carboxy(C_1-C_6)alkyl or optionally substituted heterocyclic(C_1-C_6)alkyl, said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 8 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing a sulfur atom, or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
wherein said heterocyclic group may be substituted by one or two suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro, cyano and imino-protective group,

R^5 is carboxy, protected carboxy, carboxy(C_1-C_6)alkyl or protected carboxy(C_1-C_6)alkyl,
R^6 is hydrogen or optionally substituted C_1-C_6 alkyl,
R^7 is hydrogen or C_1-C_6 alkyl, and
A is -O-, -NH-, C_1-C_6 alkylimino or C_1-C_6 alkylene, provided that when R^3 is indol-3-ylmethyl or (N-formylindol-3-yl)methyl then R^2 is not C_3-C_5 alkyl,

or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1, wherein

R^3 is heterocyclic(C_1-C_6)alkyl or C_6-C_{10} ar(C_1-C_6)alkyl, each of which is optionally substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro, cyano and imino-protective group,
said heterocyclic group being
unsaturated condensed 8 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s).

3. The compound of Claim 2, wherein

R^3 is 9- or 10-membered benzene-condensed heterocyclic (C_1-C_6)alkyl, in which the heterocyclic group contains one to three nitrogen atoms and may be substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro, cyano and imino-protective group; or C_6-C_{10} ar(C_1-C_6)alkyl.

4. The compound of Claim 3, wherein

R^5 is carboxy, esterified carboxy selected from : C_1-C_6 alkoxycarbonyl, C_6-C_{10} ar (C_1-C_6)alkoxycarbonyl and

C_6-C_{10} aroyl (C_1-C_6)alkoxycarbonyl; amidated carboxy, selected from : carbamoyl, N- or N,N-di(C_1-C_6) alkylcarbamoyl, C_1-C_6 alkylcarbamoyl substituted by one or two substituents selected from carboxy and protected carboxy, N-(C_1-C_6)alkyl-N-[carboxy- or protected carboxy(C_1-C_6)alkyl]carbamoyl, C_6-C_{10} ar (C_1-C_6)alkylcarbamoyl, carboxy- or protected carboxy-substituted C_6-C_{10} ar(C_1-C_6)alkylcarbamoyl, C_3-C_7 cycloalkylcarbamoyl, N-[carboxy- or protected carboxy-substituted C_3-C_7 cycloalkyl (C_1-C_6)alkyl]carbamoyl, C_1-C_6 alkylsulfonylcarbamoyl, C_6-C_{10} arylsulfonylcarbamoyl, carboxy- or protected carboxy-substituted 5- or 6-membered aromatic heteromonocyclic(C_1-C_6)alkylcarbamoyl, in which the heterocyclic ring contains one to three nitrogen atoms, C_3-C_{10} alkyleneaminocarbonyl, C_3-C_{10} alkyleneaminocarbonyl substituted by carboxy or protected carboxy, [C_3-C_{10} alkyleneamino(C_1-C_6)alkyl]carbamoyl substituted by one to two substituents selected from oxo, carboxy, protected carboxy and carbamoyl, morpholinocarbonyl, 5- or 6-membered saturated heteromonocycliccarbamoyl, in which the heterocyclic ring contains one nitrogen atom and one oxygen atom, 5- or 6-membered aromatic heteromonocycliccarbamoyl, in which the heterocyclic ring contains one to three nitrogen atoms, 5- or 6-membered aromatic heteromonocycliccarbamoyl, in which the heterocyclic ring contains one to two nitrogen atoms and one sulfur atom and may be substituted by C_1-C_6 alkyl, 9- or 10-membered benzene-condensed heterocyclic carbamoyl, in which the heterocyclic ring contains one to two nitrogen atoms and one sulfur atom, 5- or 6-membered saturated heteromonocyclic(C_1-C_6)alkylcarbamoyl, in which the heterocyclic ring contains one nitrogen atom and one oxygen atom, 5- or 6-membered aromatic heteromonocyclic(C_1-C_6)-alkylcarbonyl, in which the heterocyclic ring contains one to three nitrogen atoms, carbazoyl, di(C_1-C_6)alkylcarbazoyl; carboxy(C_1-C_6)alkyl; or protected carboxy(C_1-C_6)alkyl; and

R^6 is hydrogen or heterocyclic(C_1-C_6)alkyl, in which said heterocyclic group is unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s).

5. The compound of Claim 4, wherein

R^1 is carbamoyl; saturated or unsaturated, acyclic or cyclic aliphatic acyl optionally substituted by aromatic or heterocyclic group(s), aromatic acyl, or heterocyclic acyl, each of which is derived from an organic carboxylic or an organic carbonic or an organic sulfonic or an organic carbamic acid;

R^2 is C_1-C_6 alkyl; C_6-C_{10} ar(C_1-C_6)alkyl; C_3-C_7 cycloalkyl(C_1-C_6)alkyl; or 5- or 6-membered aromatic heteromonocyclic (C_1-C_6)alkyl, in which the heterocyclic ring contains one to three nitrogen atoms;

R^3 is 9- or 10-membered benzene-condensed heterocyclic (C_1-C_6)alkyl, in which the heterocyclic group contains one to three nitrogen atoms and may be substituted by C_1-C_6 alkyl or C_1-C_6 alkanoyl; or C_6-C_{10} ar (C_1-C_6)alkyl;

R^4 is C_1-C_6 alkyl; C_6-C_{10} ar(C_1-C_6)alkyl; amino(C_1-C_6)alkyl; protected amino(C_1-C_6)alkyl; carboxy(C_1-C_6)alkyl; protected carboxy(C_1-C_6)alkyl; 5- or 6-membered aromatic heteromonocyclic (C_1-C_6)alkyl, in which the heterocyclic ring contains one to three nitrogen atoms; or 5- or 6-membered aromatic heteromonocyclic (C_1-C_6)alkyl, in which the heterocyclic ring contains one or two nitrogen atoms and one sulfur atom;

R^5 is carboxy; esterified carboxy selected from: C_1-C_6 alkoxycarbonyl, C_6-C_{10} ar(C_1-C_6)alkoxycarbonyl and C_6-C_{10} aroyl (C_1-C_6)alkoxycarbonyl; amidated carboxy selected from: carbamoyl, N- or N,N-di(C_1-C_6) alkylcarbamoyl, C_1-C_6 alkylcarbamoyl substituted by one or two substituents selected from carboxy and protected carboxy, N-(C_1-C_6)alkyl-N-[carboxy- or protected carboxy(C_1-C_6)alkyl]carbamoyl, C_6-C_{10} ar (C_1-C_6)alkylcarbamoyl, carboxy- or protected carboxy-substituted C_6-C_{10} ar(C_1-C_6)alkylcarbamoyl, C_3-C_7 cycloalkylcarbamoyl, N-[carboxy- or protected carboxy-substituted C_3-C_7 cycloalkyl, (C_1-C_6)alkyl]carbamoyl, C_1-C_6 alkylsulfonylcarbamoyl, C_6-C_{10} arylsulfonylcarbamoyl, carboxy- or protected carboxy-substituted 5- or 6-membered aromatic heteromonocyclic(C_1-C_6)alkylcarbamoyl, in which the heterocyclic ring contains one to three nitrogen atoms, C_3-C_{10} alkyleneaminocarbonyl, C_3-C_{10} alkyleneaminocarbonyl substituted by carboxy or protected carboxy, [C_3-C_{10} alkyleneamino(C_1-C_6)alkyl]carbamoyl substituted by one to two substituents selected from oxo, carboxy, protected carboxy and carbamoyl, morpholinocarbonyl, 5- or 6-membered saturated heteromonocycliccarbamoyl, in which the heterocyclic ring contains one nitrogen atom and one oxygen atom, 5- or 6-membered aromatic heteromonocycliccarbamoyl, in which the heterocyclic ring contains one to three nitrogen atoms, 5- or 6-membered aromatic heteromonocycliccarbamoyl, in which the heterocyclic ring contains one to two nitrogen atoms and one sulfur atom and may be substituted by C_1-C_6 alkyl, 9- or 10-membered benzene-condensed heterocyclic carbamoyl, in which the heterocyclic ring contains one to two nitrogen atoms and one sulfur atom, 5- or 6-membered saturated heteromonocyclic(C_1-C_6)alkylcarbamoyl, in which the heterocyclic ring contains one nitrogen atom and one oxygen atom, 5- or 6-membered aromatic heteromonocyclic(C_1-C_6)alkylcarbonyl, in which the heterocyclic ring contains one to three nitrogen atoms, carbazoyl, di(C_1-C_6)alkylcarbazoyl; carboxy(C_1-C_6)alkyl; or protected carboxy(C_1-C_6)alkyl; and

R^6 is hydrogen; or
5- or 6-membered aromatic heteromonocyclic(C_1-C_6)alkyl, in which the heterocyclic ring contains one to three nitrogen atoms.

6. The compound of Claim 5, wherein

R^1 is carbamoyl; C_1-C_6 alkanoyl; amino(C_1-C_6)alkanoyl; C_1-C_6 alkoxycarbonylamino(C_1-C_6)alkanoyl; C_3-C_7 cycloalkylureido (C_1-C_6)alkanoyl; C_1-C_6 alkoxycarbonyl; C_3-C_7 cycloalkyl (C_1-C_6)alkanoyl; C_3-C_7 cycloalkylcarbonyl; C_3-C_7 cycloalkyloxycarbonyl; benzoyl; naphthoyl; phenyl(C_1-C_6)alkanoyl; naphthyl(C_1-C_6)alkanoyl; amino-substituted phenyl(C_1-C_6)alkanoyl; C_1-C_6 alkoxycarbonylamino-substituted phenyl(C_1-C_6)alkanoyl; halophenyl(C_1-C_6)alkanoyl; phenyl(C_2-C_6)alkenoyl; phenylglyoxyloyl; phenyl(C_1-C_6)alkylglyoxyloyl; pyridylcarbonyl; tetrahydropyridylcarbonyl; tetrahydroquinolylcarbonyl; tetrahydroisoquinolylcarbonyl; morpholinylcarbonyl; thiomorpholinylcarbonyl; indolylcarbonyl; piperazinylcarbonyl substituted by one to three substituents selected from oxo and C_1-C_6 alkyl; pyridyl(C_1-C_6)alkanoyl; morpholinylcarbonyl(C_1-C_6)alkanoyl; phenyl(C_1-C_6)alkylsulfonyl; N- or N,N-di(C_1-C_{10})alkylcarbamoyl; hydroxy(C_1-C_6)alkylcarbamoyl; carboxy(C_1-C_6)alkylcarbamoyl; C_1-C_6 alkoxycarbonyl(C_1-C_6)alkylcarbamoyl; carbamoyl(C_1-C_6)alkylcarbamoyl; [N- or N,N-di(C_1-C_6) alkylcarbamoyl](C_1-C_6)alkylcarbamoyl; N-C_1-C_6 alkyl-N-[hydroxy(C_1-C_6)alkyl]carbamoyl; N-C_1-C_6 alkyl-N-[di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl]carbamoyl; C_3-C_{10} alkyleneaminocarbonyl; di(C_1-C_6) alkylcarbamoyl(C_3-C_{10})alkyleneaminocarbonyl; N-C_1-C_6 alkyl-N-(C_3-C_7)cycloalkylcarbamoyl; mono- or di(C_3-C_7)cycloalkylcarbamoyl; hydroxy- or di(C_1-C_6)alkylcarbamoyl- or di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl-substituted (C_3-C_7)cycloalkylcarbamoyl; C_3-C_7 cycloalkyl (C_1-C_6)alkylcarbamoyl; di(C_1-C_6)alkylcarbamoyl-substituted C_3-C_7 cycloalkyl (C_1-C_6)alkylcarbamoyl; di(C_1-C_6) alkylcarbamoyl-substituted phenyl(C_1-C_6)alkylcarbamoyl; phenylcarbamoyl, in which the phenyl group may be substituted by one to three substituents selected from halogen, C_1-C_6 alkyl and C_1-C_6 alkoxy; pyridylcarbamoyl; N-C_1-C_6 alkoxycarbonylpiperidylcarbamoyl; morpholinyl(C_1-C_6)alkylcarbamoyl; C_1-C_6 alkanoylcarbazoyl; C_3-C_{10} alkyleneaminocarbamoyl; N-(C_3-C_7)cycloalkylcarbamoyl(C_1-C_6)alkylcarbamoyl; C_3-C_{10} alkyleneaminocarbonyl (C_1-C_6)alkylcarbamoyl; pyridyl(C_1-C_6)alkylcarbamoyl; or oxo-substituted hexahydroazepinylcarbamoyl;

R^2 is C_1-C_6 alkyl;

R^3 is indolyl(C_1-C_6)alkyl;
N-(C_1-C_6)alkylindolyl(C_1-C_6)alkyl; N-(C_1-C_6)alkanoylindolyl(C_1-C_6)alkyl; phenyl(C_1-C_6)alkyl; or naphthyl(C_1-C_6)alkyl;

R^4 is C_1-C_6 alkyl;
amino(C_1-C_6)alkyl; mono- or di- or triphenyl(C_1-C_6)alkoxycarbonylamino(C_1-C_6)alkyl; carboxy(C_1-C_6)alkyl; mono- or di or triphenyl(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl; phenyl(C_1-C_6)alkyl; naphthyl (C_1-C_6)alkyl; pyridyl(C_1-C_6)alkyl; imidazolyl(C_1-C_6)alkyl; or thiazolyl(C_1-C_6)alkyl;

R^5 is carboxy;
C_1-C_6 alkoxycarbonyl; mono- or di- or triphenyl(C_1-C_6)alkoxycarbonyl; benzoyl(C_1-C_6)alkoxycarbonyl; carbamoyl; N- or N,N-di(C_1-C_6)alkylcarbamoyl; C_1-C_6 alkylcarbamoyl substituted by one or two substituents selected from carboxy, C_1-C_6 alkoxycarbonyl, mono or di or triphenyl(C_1-C_6)-alkoxycarbonyl and benzoyl(C_1-C_6)alkoxycarbonyl); N-(C_1-C_6)alkyl-N-[carboxy(or C_1-C_6 alkoxycarbonyl)(C_1-C_6)alkyl]carbamoyl; phenyl(C_1-C_6)alkylcarbamoyl; carboxy- or C_1-C_6 alkoxycarbonyl-substituted phenyl(C_1-C_6)alkylcarbamoyl; C_3-C_7 cycloalkylcarbamoyl; carboxy(C_3-C_7)cycloalkyl(C_1-C_6)alkyl] carbamoyl; C_1-C_6 alkoxycarbonyl (C_3-C_7)cycloalkyl(C_1-C_6)alkyl]carbamoyl; C_1-C_6 alkylsulfonylcarbamoyl; phenylsulfonylcarbamoyl, carboxy- or C_1-C_6 alkoxycarbonyl-substituted pyridyl(C_1-C_6)alkylcarbamoyl; C_3-C_{10} alkyleneaminocarbonyl; C_3-C_{10} alkyleneaminocarbonyl substituted by carboxy or C_1-C_6 alkoxycarbonyl; [C_3-C_{10} alkyleneamino (C_1-C_6)alkyl]carbamoyl substituted by one to two substituents selected from oxo, carboxy, C_1-C_6 alkoxycarbonyl and carbamoyl; morpholinocarbonyl; morpholinylcarbamoyl; pyridylcarbamoyl; thiazolylcarbamoyl; C_1-C_6 alkylthiadiazolylcarbamoyl; benzothiazolylcarbamoyl; morpholinyl(C_1-C_6)alkylcarbamoyl; pyridyl(C_1-C_6)alkylcarbamoyl; carbazoyl, di(C_1-C_6)alkylcarbazoyl; carboxy(C_1-C_6)alkyl; C_1-C_6 alkoxycarbonyl(C_1-C_6)alkyl; or benzoyl (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl, and

R^6 and R^7 are each hydrogen.

7. The compound of Claim 6, wherein

R^1 is N- or N,N-di(C_1-C_{10})alkylcarbamoyl, N-C_1-C_6 alkyl-N-(C_3-C_7)cycloalkylcarbamoyl, N- or N,N-di(C_3-C_7)

cycloalkylcarbamoyl, N-(C_1-C_6)alkyl-N-[N,N-di(C_1-C_6)alkylcarbamoyl (C_1-C_6)alkyl]carbamoyl, phenylcarbamoyl, C_3-C_{10} alkyleneaminocarbonyl or N-(C_1-C_6)alkyl-N-[hydroxy(C_1-C_6)alkyl]carbamoyl,

R^2 is C_1-C_6 alkyl,

R^3 is indolyl(C_1-C_6)alkyl,
N-(C_1-C_6)alkanoylindolyl(C_1-C_6)alkyl or N-(C_1-C_6)alkylindolyl(C_1-C_6)alkyl,

R^4 is pyridyl(C_1-C_6)alkyl or phenyl(C_1-C_6)alkyl,

R^5 is carboxy,
C_1-C_6 alkoxycarbonyl,
carbamoyl or
N- or N,N-di(C_1-C_6)alkylcarbamoyl, and

A is methylene or -NH-.

8. The compound of Claim 7, wherein

R^1 is isopropylcarbamoyl, 2-methylbutylcarbamoyl, heptylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, diisopropylcarbamoyl, dibutylcarbamoyl, diisobutylcarbamoyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, 3,5- or 2,6-dimethylpiperidin-1-ylcarbonyl, hexahydro-1H-azepin-1-ylcarbonyl or octahydroazocin-1-ylcarbonyl,

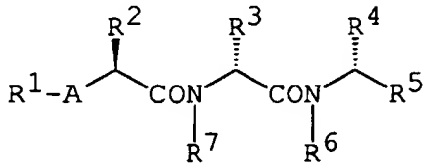
R^2 is isobutyl,

R^3 is indol-3-ylmethyl, N-formylindol-3-ylmethyl, N-methylindol-3-ylmethyl, N-ethylindol-3-ylmethyl, N-propylindol-3-ylmethyl or N-isobutylindol-3-yl-methyl,

R^4 is 2-pyridylmethyl or benzyl,

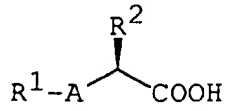
R^5 is carboxy, methoxycarbonyl, ethoxycarbonyl, carbamoyl, methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, N,N-dimethylcarbamoyl or N,N-diethylcarbamoyl.

9. A process for the preparation of a peptide compound of the formula (I):



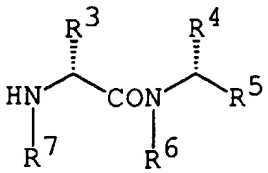
in which R^1, R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined in Claim 1,
or salts thereof, which comprises

(a) reacting a compound of the formula:



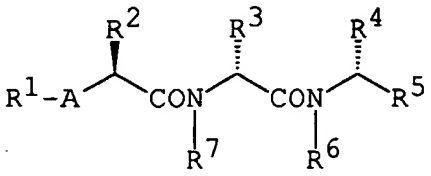
(II)

wherein R^1, R^2 and A are each as defined above, or its reactive derivative at the carboxy group or a salt thereof, with a compound of the formula:



(III)

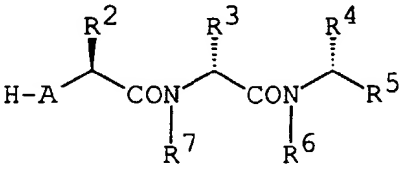
wherein R^3, R^4, R^5, R^6 and R^7 are each as defined above, or its reactive derivative at the amino group, or a salt thereof, to give a compound of the formula:



(I)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above,
or a salt thereof; or

(b) reacting a compound of the formula:

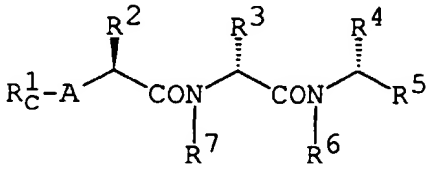


(I-a)

wherein R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above,
or its reactive derivative at the amino group, or a salt thereof, with a compound of the formula:

$$R_c^1\text{-OH} \qquad \text{(IV)}$$

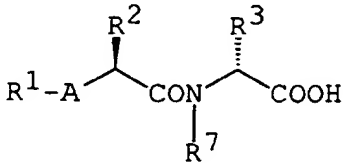
wherein R_c^1 is acyl,
or its reactive derivative at the carboxy group, or a salt thereof, to give a compound of the formula:



(I-b)

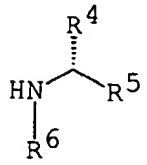
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above,
or a salt thereof; or

(c) reacting a compound of the formula:



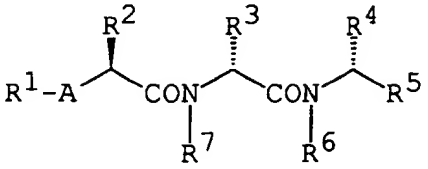
(V)

wherein R^1, R^2, R^3, R^7 and A are each as defined above, or its reactive derivative at the carboxy group, or a salt thereof, with a compound of the formula:



(VI)

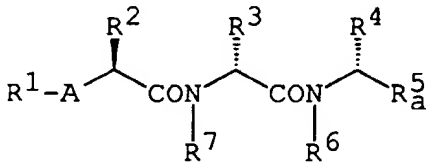
wherein R^4, R^5 and R^6 are each as defined above, or its reactive derivative at the amino group, or a salt thereof, to give a compound of the formula:



(I)

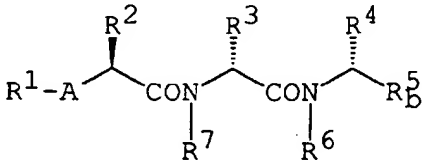
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above,
or a salt thereof; or

(d) subjecting a compound of the formula:



(I-c)

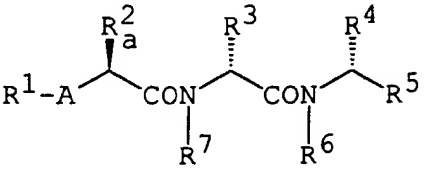
wherein R^1, R^2, R^3, R^4, R^6, R^7 and A are each as defined above, and
R^5_a is protected carboxy or protected carboxy(C_1-C_6)alkyl,
or a salt thereof, to a removal reaction of the carboxy-protective group to give a compound of the formula:



(I-d)

wherein R^1, R^2, R^3, R^4, R^6, R^7 and A are each as defined above, and
R^5_b is carboxy or carboxy(C_1-C_6)alkyl,
or a salt thereof; or

(e) subjecting a compound of the formula:



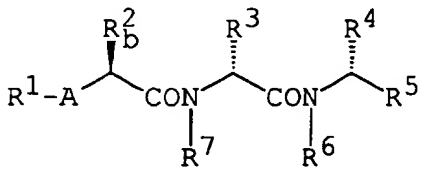
(I-e)

in which R^1, R^3, R^4, R^5, R^6, R^7 and A are each as defined above, and

R_a^2 is protected imino containing heterocyclic(C_1-C_6)alkyl optionally substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro and cyano; said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

or a salt thereof, to removal reaction of the imino-protective group in R_a^2 to give a compound of the formula:



(I-f)

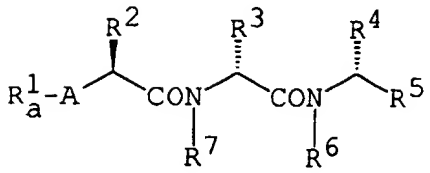
in which R^1, R^3, R^4, R^5, R^6, R^7 and A are each as defined above, and

R_b^2 is imino containing heterocyclic(C_1-C_6)alkyl optionally substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro and cyano; said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

or a salt thereof; or

(f) subjecting a compound of the formula:

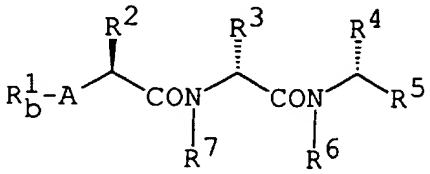


(I-g)

in which R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above, and

R^2_a is acyl substituted by a protected amino group,

or a salt thereof, to removal reaction of the amino-protective group to give a compound of the formula:

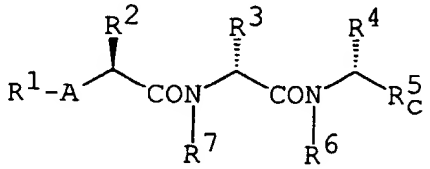


(I-h)

in which R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above, and

R^1_b is acyl substituted by an amino group, or a salt thereof; or

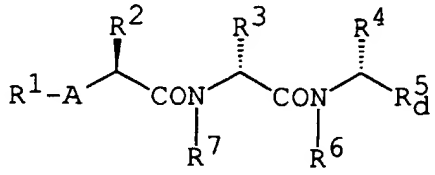
(g) reacting a compound of the formula:



(I-i)

in which R^1, R^2, R^3, R^4, R^6, R^7 and A are each as defined above, and

R^5_c is esterified carboxy as defined in Claim 4, or its reactive derivative at the carboxy group, or a salt thereof, with an optionally substituted amine, or a salt thereof to give a compound of the formula:



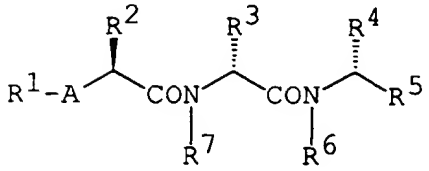
(I-j)

in which R^1, R^2, R^3, R^4, R^6, R^7 and A are each as defined above, and

R^5_d is amidated carboxy as defined in Claim 4,

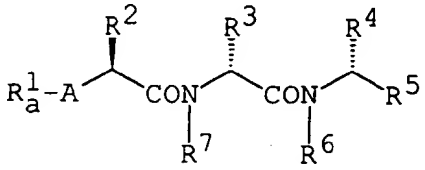
or a salt thereof; or

(h) acylating the amino group in R^1_b of a compound of the formula:



(I-h)

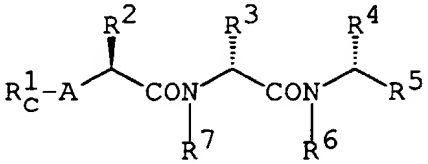
in which R^1_b, R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above, or a salt thereof, to give compound of the formula:



(I-g)

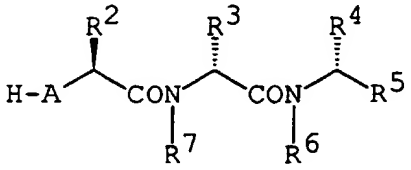
in which R^1_a, R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above, or a salt thereof; or

(i) subjecting a compound of the formula:



(I-b)

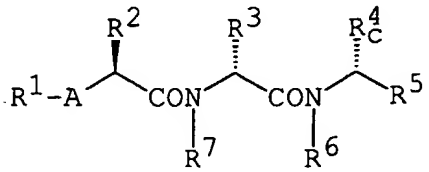
in which R^1_c, R^2, R^3, R^4, R^6, R^7 and A are each as defined above, or a salt thereof, to a removal reaction of the acyl group of R^1_c to give a compound of the formula:



(I-a)

in which R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above, or a salt thereof; or

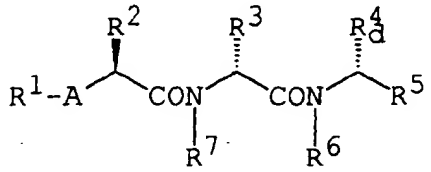
(j) subjecting a compound of the formula:



(I-k)

in which R^1, R^2, R^3, R^5, R^6, R^7 and A are each as defined above, and

R^4_c is protected carboxy(C_1-C_6)alkyl, or a salt thereof, to a removal reaction of the carboxy-protective group in R^4_c to give a compound of the formula:



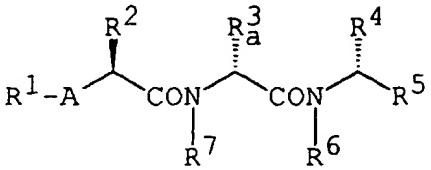
(I-l)

in which R^1, R^2, R^3, R^5, R^6, R^7 and A are each as defined above, and

R^4_d is carboxy(C_1-C_6)alkyl,

or a salt thereof; or

(k) subjecting a compound of the formula:



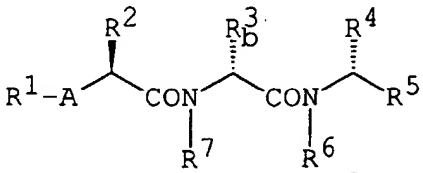
(I-m)

wherein R^1, R^2, R^4, R^5, R^6, R^7 and A are each as defined above, and

R^3_a is protected imino containing heterocyclic(C_1-C_6)alkyl optionally substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro and cyano, said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

or a salt thereof, to a removal reaction of the imino-protective group in R^3_a to give a compound of the formula:



(I-n)

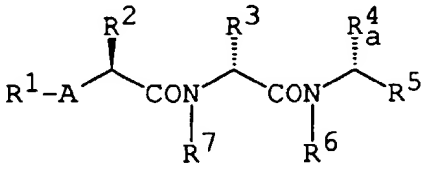
wherein R^1, R^2, R^4, R^5, R^6, R^7 and A are each as defined above, and

R^3_b is imino containing heterocyclic(C_1-C_6)alkyl optionally substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro and cyano, said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

or a salt thereof; or

(1) subjecting a compound of the formula:



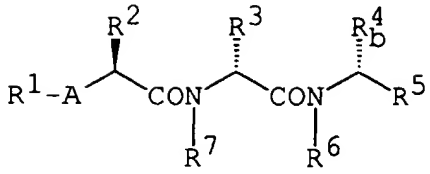
(I-o)

in which R^1, R^2, R^3, R^5, R^6, R^7 and A are each as defined above, and

R^4_a is protected amino(C_1-C_6)alkyl or protected imino containing heterocyclic(C_1-C_6)-alkyl, said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 8 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
wherein said heterocyclic group may be substituted by one or two suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro and cyano,

or a salt thereof, to removal reaction of the amino or imino-protective group in R^4_a to give a compound of the formula:



(I-p)

in which R^1, R^2, R^3, R^5, R^6, R^7 and A are each as defined above, and
R^4_b is amino(C_1-C_6)alkyl or imino containing heterocyclic(C_1-C_6)alkyl,
said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom (s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom (s), or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
wherein said heterocyclic group may be substituted by one or two suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro and cyano,

or a salt thereof.

10. A pharmaceutical composition which comprises a compound of Claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

11. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 or pharmaceutically acceptable salts thereof with a pharmaceutically acceptable carrier or excipient.

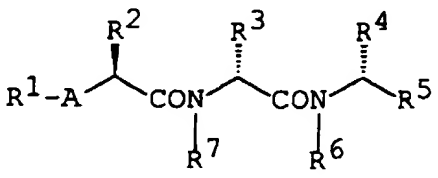
12. A compound of Claim 1 or pharmaceutically acceptable salts thereof for use as a medicament.

13. A compound of Claim 1 or pharmaceutically acceptable salts thereof for use as an endothelin antagonistic agent.

14. A use of a compound of Claim 1 or pharmaceutically acceptable salts thereof for manufacturing a medicament for treating endothelin mediated diseases.

Claims for the following Contracting States : ES, GR

1. A process for preparing a peptide compound of the formula (I):



(I)

having endothelin receptor antagonistic activity,
in which

R^1 is hydrogen or acyl,

R^2 is C_1-C_6 alkyl;
C_6-C_{10} ar(C_1-C_6)alkyl optionally substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro and cyano; cyclo(C_1-C_6)alkyl(C_1-C_6)alkyl; or heterocyclic(C_1-C_6)alkyl optionally substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro, cyano and imino-protective group;
said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8 membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing a sulfur atom, or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

R^3 is heterocyclic(C_1-C_6)alkyl or
C_6-C_{10} ar(C_1-C_6)alkyl, each of which is optionally substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro, cyano and imino-protective group,
said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 8 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing a sulfur atom, or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

R^4 is C_1-C_6 alkyl, C_6-C_{10} ar(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, protected amino(C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl, protected carboxy(C_1-C_6)alkyl or optionally substituted heterocyclic(C_1-C_6)alkyl, said heterocyclic group being

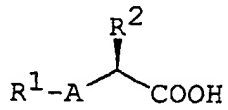
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 8 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing a sulfur atom, or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
wherein said heterocyclic group may be substituted by one or two suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro, cyano and imino-protective group,

R^5 is carboxy, protected carboxy, carboxy(C_1-C_6)alkyl or protected carboxy(C_1-C_6)alkyl,
R^6 is hydrogen or optionally substituted C_1-C_6 alkyl,
R^7 is hydrogen or C_1-C_6 alkyl, and
A is -O-, -NH-, C_1-C_6 alkylimino or C_1-C_6 alkylene, provided that when R^3 is indol-3-ylmethyl or (N-formylindol-3-yl)methyl then R^2 is not C_3-C_5 alkyl,

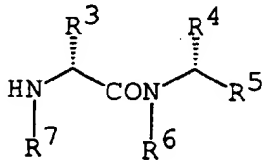
or a pharmaceutically acceptable salt thereof,
which comprises

(a) reacting a compound of the formula:



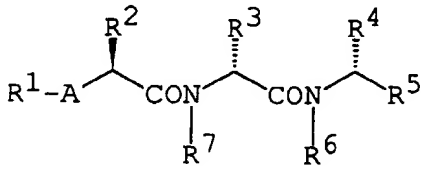
(II)

wherein R^1, R^2 and A are each as defined above, or its reactive derivative at the carboxy group or a salt thereof, with a compound of the formula:



(III)

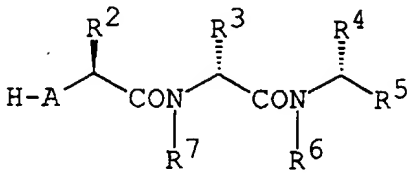
wherein R^3, R^4, R^5, R^6 and R^7 are each as defined above, or its reactive derivative at the amino group, or a salt thereof, to give a compound of the formula:



(I)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above,
or a salt thereof; or

(b) reacting a compound of the formula:

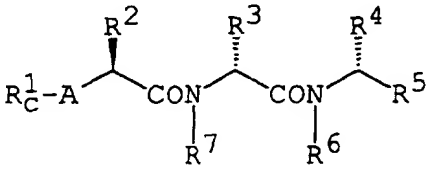


(I-a)

wherein R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above,
or its reactive derivative at the amino group, or a salt thereof, with a compound of the formula:

(IV)

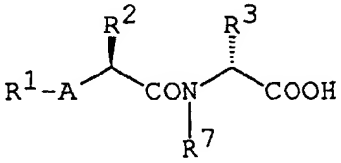
wherein R^1_c is acyl,
or its reactive derivative at the carboxy group, or a salt thereof, to give a compound of the formula:



(I-b)

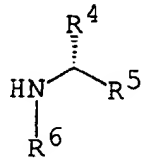
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above,
or a salt thereof; or

(c) reacting a compound of the formula:



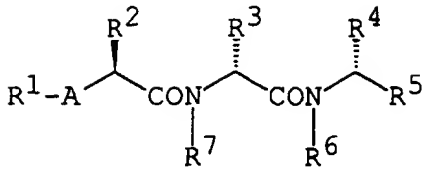
(V)

wherein R^1, R^2, R^3, R^7 and A are each as defined above, or its reactive derivative at the carboxy group, or a salt thereof, with a compound of the formula:



(VI)

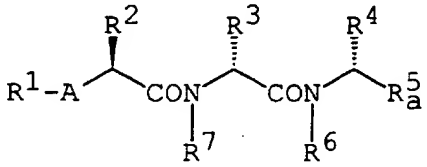
wherein R^4, R^5 and R^6 are each as defined above, or its reactive derivative at the amino group, or a salt thereof, to give a compound of the formula:



(I)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above,
or a salt thereof; or

(d) subjecting a compound of the formula:

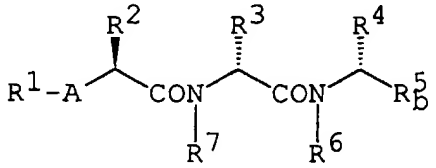


(I-c)

wherein R^1, R^2, R^3, R^4, R^6, R^7 and A are each as defined above, and

R^5_a is protected carboxy or protected carboxy(C_1-C_6)alkyl,

or a salt thereof, to a removal reaction of the carboxy-protective group to give a compound of the formula:



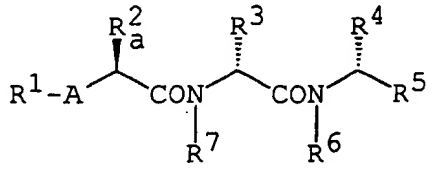
(I-d)

wherein R^1, R^2, R^3, R^4, R^6, R^7 and A are each as defined above, and

R^5_b is carboxy or carboxy(C_1-C_6)alkyl,

or a salt thereof; or

(e) subjecting a compound of the formula:



(I-e)

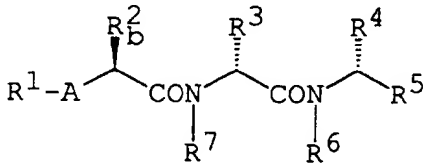
in which R^1, R^3, R^4, R^5, R^6, R^7 and A are each as defined above, and

R^2_a is protected imino containing heterocyclic(C_1-C_6)alkyl optionally substituted by suitable substituent (s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro and

cyano;
said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

or a salt thereof, to removal reaction of the imino-protective group in R_a^2 to give a compound of the formula:



(I-f)

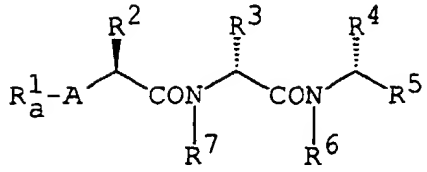
in which R^1, R^3, R^4, R^5, R^6, R^7 and A are each as defined above, and

R_b^2 is imino containing heterocyclic(C_1-C_6)alkyl optionally substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro and cyano;
said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

or a salt thereof; or

(f) subjecting a compound of the formula:

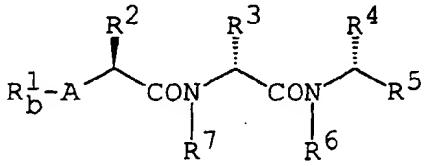


(I-g)

in which R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above, and

R^1_a is acyl substituted by a protected amino group,

or a salt thereof, to removal reaction of the amino-protective group to give a compound of the formula:

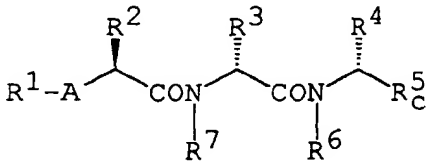


(I-h)

in which R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above, and

R^1_b is acyl substituted by an amino group, or a salt thereof; or

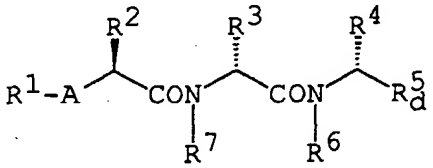
(g) reacting a compound of the formula:



(I-i)

in which R^1, R^2, R^3, R^4, R^6, R^7 and A are each as defined above, and

R^5_c is esterified carboxy as defined in Claim 4, or its reactive derivative at the carboxy group, or a salt thereof, with an optionally substituted amine, or a salt thereof to give a compound of the formula:

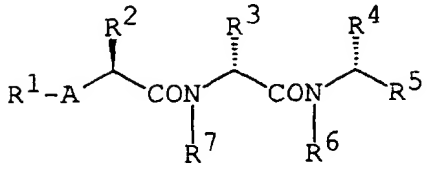


(I-j)

in which R^1, R^2, R^3, R^4, R^6, R^7 and A are each as defined above, and

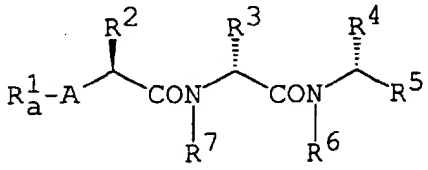
R^5_d is amidated carboxy as defined in Claim 4, or a salt thereof; or

(h) acylating the amino group in R^1_b of a compound of the formula:



(I-h)

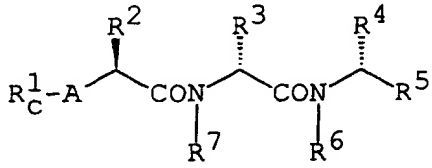
in which R^1_b, R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above, or a salt thereof, to give compound of the formula:



(I-g)

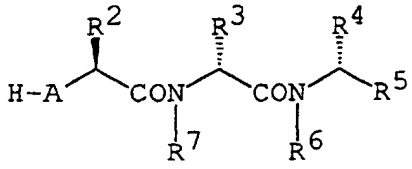
in which R^1_a, R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above, or a salt thereof; or

(i) subjecting a compound of the formula:



(I-b)

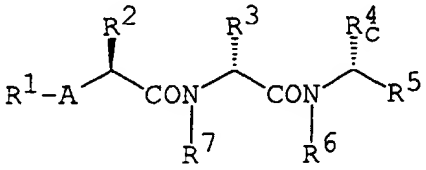
in which R^1_c, R^2, R^3, R^4, R^6, R^7 and A are each as defined above, or a salt thereof, to a removal reaction of the acyl group of R^1_c to give a compound of the formula:



(I-a)

in which R^2, R^3, R^4, R^5, R^6, R^7 and A are each as defined above, or a salt thereof; or

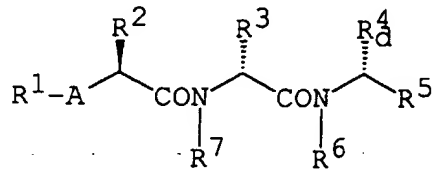
(j) subjecting a compound of the formula:



(I-k)

in which R^1, R^2, R^3, R^5, R^6, R^7 and A are each as defined above, and

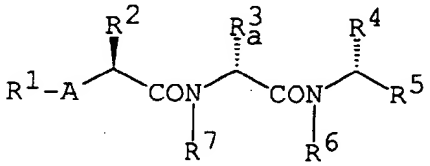
R^4_c is protected carboxy(C_1-C_6)alkyl, or a salt thereof, to a removal reaction of the carboxy-protective group in R^4_c to give a compound of the formula:



(I-l)

in which R^1, R^2, R^3, R^5, R^6, R^7 and A are each as defined above, and
R^4_d is carboxy(C_1-C_6)alkyl,
or a salt thereof; or

(k) subjecting a compound of the formula:



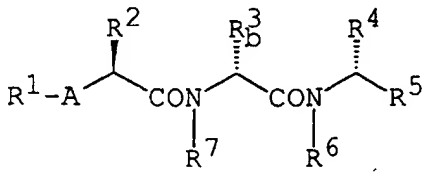
(I-m)

wherein R^1, R^2, R^4, R^5, R^6, R^7 and A are each as defined above, and

R^3_a is protected imino containing heterocyclic(C_1-C_6)alkyl optionally substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro and cyano, said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

or a salt thereof, to a removal reaction of the imino-protective group in R^3_a to give a compound of the formula:



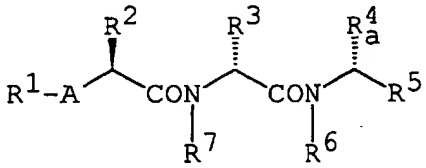
(I-n)

wherein R^1, R^2, R^4, R^5, R^6, R^7 and A are each as defined above, and

R^3_b is imino containing heterocyclic(C_1-C_6)alkyl optionally substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro and cyano,
said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

or a salt thereof; or
(1) subjecting a compound of the formula:



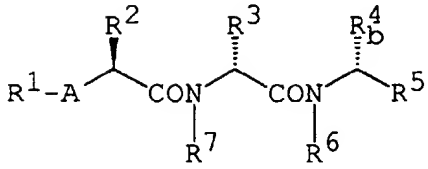
(I-o)

in which R^1, R^2, R^3, R^5, R^6, R^7 and A are each as defined above, and

R^4_a is protected amino(C_1-C_6)alkyl or protected imino containing heterocyclic(C_1-C_6)-alkyl, said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 8 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
wherein said heterocyclic group may be substituted by one or two suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro and cyano,

or a salt thereof, to removal reaction of the amino or imino-protective group in R^4_a to give a compound of the formula:



(I-p)

in which R^1, R^2, R^3, R^5, R^6, R^7 and A are each as defined above, and

R^4_b is amino(C_1-C_6)alkyl or imino containing heterocyclic(C_1-C_6)alkyl,
said heterocyclic group being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), or
unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),
wherein said heterocyclic group may be substituted by one or two suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro and cyano,

or a salt thereof.

2. The process of Claim 1, wherein

R^3 is heterocyclic(C_1-C_6)alkyl or C_6-C_{10} ar(C_1-C_6)alkyl, each of which is optionally substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro, cyano and imino-protective group,
said heterocyclic group being
unsaturated condensed 8 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s).

3. The process of Claim 2, wherein

R^3 is 9- or 10-membered benzene-condensed heterocyclic (C_1-C_6)alkyl, in which the heterocyclic group contains one to three nitrogen atoms and may be substituted by suitable substituent(s) selected from hydroxy, protected hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, amino, nitro, cyano and imino-protective group; or C_6-C_{10} ar(C_1-C_6)alkyl.

4. The process of Claim 3, wherein

R^5 is carboxy, esterified carboxy selected from : C_1-C_6 alkoxycarbonyl, C_6-C_{10} ar(C_1-C_6)alkoxycarbonyl and C_6-C_{10} aroyl(C_1-C_6)alkoxycarbonyl; amidated carboxy, selected from :

carbamoyl,
N- or N,N-di(C_1-C_6)alkylcarbamoyl, C_1-C_6 alkylcarbamoyl substituted by one or two substituents selected from carboxy and protected carboxy,
N-(C_1-C_6)alkyl-N-[carboxy- or protected carboxy(C_1-C_6)alkyl]carbamoyl, C_6-C_{10} ar(C_1-C_6)alkylcar-

bamoyl, carboxy- or protected carboxy-substituted C_6-C_{10} ar(C_1-C_6)alkylcarbamoyl, C_3-C_7 cycloalkylcarbamoyl,
N-[carboxy- or protected carboxy-substituted C_3-C_7 cycloalkyl (C_1-C_6)alkyl]carbamoyl, C_1-C_6 alkylsulfonylcarbamoyl, C_6-C_{10} arylsulfonylcarbamoyl, carboxy- or protected carboxy-substituted 5- or 6-membered aromatic heteromonocyclic(C_1-C_6)alkylcarbamoyl, in which the heterocyclic ring contains one to three nitrogen atoms, C_3-C_{10} alkyleneaminocarbonyl, C_3-C_{10} alkyleneaminocarbonyl substituted by carboxy or protected carboxy, [C_3-C_{10} alkyleneamino(C_1-C_6)alkyl]carbamoyl substituted by one to two substituents selected from oxo, carboxy, protected carboxy and carbamoyl, morpholinocarbonyl,
5- or 6-membered saturated heteromonocycliccarbamoyl, in which the heterocyclic ring contains one nitrogen atom and one oxygen atom,
5- or 6-membered aromatic heteromonocycliccarbamoyl, in which the heterocyclic ring contains one to three nitrogen atoms,
5- or 6-membered aromatic heteromonocycliccarbamoyl, in which the heterocyclic ring contains one to two nitrogen atoms and one sulfur atom and may be substituted by C_1-C_6 alkyl, 9- or 10-membered benzene-condensed heterocyclic carbamoyl, in which the heterocyclic ring contains one to two nitrogen atoms and one sulfur atom, 5- or 6-membered saturated heteromonocyclic(C_1-C_6)alkylcarbamoyl, in which the heterocyclic ring contains one nitrogen atom and one oxygen atom,
5- or 6-membered aromatic heteromonocyclic(C_1-C_6)alkylcarbonyl, in which the heterocyclic ring contains one to three nitrogen atoms, carbazoyl, di(C_1-C_6)alkylcarbazoyl;
carboxy(C_1-C_6)alkyl; or
protected carboxy(C_1-C_6)alkyl; and

R^6 is hydrogen or heterocyclic(C_1-C_6)alkyl, in which said heterocyclic group is unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s).

5. The process of Claim 4, wherein

R^1 is carbamoyl; saturated or unsaturated, acyclic or cyclic aliphatic acyl optionally substituted by aromatic or heterocyclic group(s), aromatic acyl, or heterocyclic acyl, each of which is derived from an organic carboxylic or an organic carbonic or an organic sulfonic or an organic carbamic acid;
R^2 is C_1-C_6 alkyl; C_6-C_{10} ar(C_1-C_6)alkyl; C_3-C_7 cycloalkyl(C_1-C_6)alkyl; or 5- or 6-membered aromatic heteromonocyclic (C_1-C_6)alkyl, in which the heterocyclic ring contains one to three nitrogen atoms;
R^3 is 9- or 10-membered benzene-condensed heterocyclic (C_1-C_6)alkyl, in which the heterocyclic group contains one to three nitrogen atoms and may be substituted by C_1-C_6 alkyl or C_1-C_6 alkanoyl; or C_6-C_{10} ar (C_1-C_6)alkyl;
R^4 is C_1-C_6 alkyl; C_6-C_{10} ar(C_1-C_6)alkyl; amino(C_1-C_6)alkyl; protected amino(C_1-C_6)alkyl; carboxy(C_1-C_6)alkyl; protected carboxy(C_1-C_6)alkyl; 5- or 6-membered aromatic heteromonocyclic (C_1-C_6)alkyl, in which the heterocyclic ring contains one to three nitrogen atoms; or 5- or 6-membered aromatic heteromonocyclic (C_1-C_6)alkyl, in which the heterocyclic ring contains one or two nitrogen atoms and one sulfur atom;
R^5 is carboxy;
esterified carboxy selected from:
C_1-C_6 alkoxycarbonyl, C_6-C_{10} ar(C_1-C_6)alkoxycarbonyl and C_6-C_{10} aroyl (C_1-C_6)alkoxycarbonyl; amidated carboxy selected from:

carbamoyl,
N- or N,N-di(C_1-C_6)alkylcarbamoyl, C_1-C_6 alkylcarbamoyl substituted by one or two substituents selected from carboxy and protected carboxy,
N-(C_1-C_6)alkyl-N-[carboxy- or protected carboxy(C_1-C_6)alkyl]carbamoyl, C_6-C_{10} ar(C_1-C_6)alkylcarbamoyl, carboxy- or protected carboxy-substituted C_6-C_{10} ar(C_1-C_6)alkylcarbamoyl, C_3-C_7 cycloalkylcarbamoyl,
N-[carboxy- or protected carboxy-substituted C_3-C_7 cycloalkyl(C_1-C_6)alkyl]carbamoyl, C_1-C_6 alkylsulfonylcarbamoyl, C_6-C_{10} arylsulfonylcarbamoyl,
carboxy- or protected carboxy-substituted 5- or 6-membered aromatic heteromonocyclic(C_1-C_6)alkylcarbamoyl, in which the heterocyclic ring contains one to three nitrogen atoms,
C_3-C_{10} alkyleneaminocarbonyl,
C_3-C_{10} alkyleneaminocarbonyl substituted by carboxy or protected carboxy,
[C_3-C_{10} alkyleneamino(C_1-C_6)alkyl]carbamoyl substituted by one to two substituents selected from

oxo, carboxy, protected carboxy and carbamoyl, morpholinocarbonyl,
5- or 6-membered saturated heteromonocycliccarbamoyl, in which the heterocyclic ring contains one nitrogen atom and one oxygen atom,
5- or 6-membered aromatic heteromonocycliccarbamoyl, in which the heterocyclic ring contains one to three nitrogen atoms,
5- or 6-membered aromatic heteromonocycliccarbamoyl, in which the heterocyclic ring contains one to two nitrogen atoms and one sulfur atom and may be substituted by C_1-C_6 alkyl, 9- or 10-membered benzene-condensed heterocyclic carbamoyl, in which the heterocyclic ring contains one to two nitrogen atoms and one sulfur atom, 5- or 6-membered saturated heteromonocyclic(C_1-C_6)-alkylcarbamoyl, in which the heterocyclic ring contains one nitrogen atom and one oxygen atom,
5- or 6-membered aromatic heteromonocyclic(C_1-C_6)alkylcarbonyl, in which the heterocyclic ring contains one to three nitrogen atoms, carbazoyl, di(C_1-C_6)alkylcarbazoyl;
carboxy(C_1-C_6)alkyl; or
protected carboxy(C_1-C_6)alkyl; and

R^6 is hydrogen; or
5- or 6-membered aromatic heteromonocyclic(C_1-C_6)alkyl, in which the heterocyclic ring contains one to three nitrogen atoms.

6. The process of Claim 5, wherein

R^1 is carbamoyl;
C_1-C_6 alkanoyl; amino(C_1-C_6)alkanoyl; C_1-C_6 alkoxycarbonylamino(C_1-C_6)alkanoyl; C_3-C_7 cycloalkylureido(C_1-C_6)alkanoyl; C_1-C_6 alkoxycarbonyl; C_3-C_7 cycloalkyl (C_1-C_6)alkanoyl; C_3-C_7 cycloalkylcarbonyl; C_3-C_7 cycloalkyloxycarbonyl; benzoyl; naphthoyl; phenyl(C_1-C_6)alkanoyl; naphthyl (C_1-C_6)alkanoyl; amino-substituted phenyl(C_1-C_6)alkanoyl; C_1-C_6 alkoxycarbonylamino-substituted phenyl(C_1-C_6)alkanoyl; halophenyl(C_1-C_6)alkanoyl; phenyl(C_2-C_6)alkenoyl; phenylglyoxyloyl; phenyl(C_1-C_6)alkylglyoxyloyl; pyridylcarbonyl; tetrahydropyridylcarbonyl; tetrahydroquinolylcarbonyl; tetrahydroisoquinolylcarbonyl; morpholinylcarbonyl; thiomorpholinylcarbonyl; indolylcarbonyl; piperazinylcarbonyl substituted by one to three substituents selected from oxo and C_1-C_6 alkyl; pyridyl (C_1-C_6)alkanoyl; morpholinylcarbonyl(C_1-C_6)alkanoyl; phenyl(C_1-C_6)alkylsulfonyl; N- or N,N-di(C_1-C_{10})alkylcarbamoyl; hydroxy(C_1-C_6)alkylcarbamoyl; carboxy(C_1-C_6)alkylcarbamoyl; C_1-C_6 alkoxycarbonyl(C_1-C_6)alkylcarbamoyl; carbamoyl(C_1-C_6)alkylcarbamoyl; [N- or N,N-di(C_1-C_6)alkylcarbamoyl](C_1-C_6)alkylcarbamoyl; N-C_1-C_6 alkyl-N-[hydroxy(C_1-C_6)alkyl]carbamoyl; N-C_1-C_6 alkyl-N-[di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl]carbamoyl; C_3-C_{10} alkyleneaminocarbonyl; di(C_1-C_6)alkylcarbamoyl(C_3-C_{10})alkyleneaminocarbonyl; N-C_1-C_6 alkyl-N-(C_3-C_7)cycloalkylcarbamoyl; mono- or di (C_3-C_7)cycloalkylcarbamoyl; hydroxy- or di(C_1-C_6)alkylcarbamoyl- or di(C_1-C_6)alkylcarbamoyl (C_1-C_6)alkyl-substituted (C_3-C_7)cycloalkylcarbamoyl; C_3-C_7 cycloalkyl (C_1-C_6)alkylcarbamoyl; di(C_1-C_6) alkylcarbamoyl-substituted C_3-C_7 cycloalkyl (C_1-C_6)alkylcarbamoyl; di(C_1-C_6)alkylcarbamoyl-substituted phenyl(C_1-C_6)alkylcarbamoyl; phenylcarbamoyl, in which the phenyl group may be substituted by one to three substituents selected from halogen, C_1-C_6 alkyl and C_1-C_6 alkoxy; pyridylcarbamoyl; N-C_1-C_6 alkoxycarbonylpiperidylcarbamoyl; morpholinyl(C_1-C_6)alkylcarbamoyl; C_1-C_6 alkanoylcarbazoyl; C_3-C_{10} alkyleneaminocarbamoyl; N-(C_3-C_7)cycloalkylcarbamoyl(C_1-C_6)alkylcarbamoyl; C_3-C_{10} alkyleneaminocarbonyl (C_1-C_6)alkylcarbamoyl; pyridyl(C_1-C_6)alkylcarbamoyl; or oxo-substituted hexahydroazepinylcarbamoyl;

R^2 is C_1-C_6 alkyl;

R^3 is indolyl(C_1-C_6)alkyl;
N-(C_1-C_6)alkylindolyl(C_1-C_6)alkyl; N-(C_1-C_6)alkanoylindolyl(C_1-C_6)alkyl; phenyl(C_1-C_6)alkyl; or naphthyl(C_1-C_6)alkyl;

R^4 is C_1-C_6 alkyl;
amino(C_1-C_6)alkyl; mono- or di- or triphenyl(C_1-C_6)alkoxycarbonylamino(C_1-C_6)alkyl; carboxy(C_1-C_6)alkyl; mono- or di or triphenyl(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl; phenyl(C_1-C_6)alkyl; naphthyl (C_1-C_6)alkyl; pyridyl(C_1-C_6)alkyl; imidazolyl(C_1-C_6)alkyl; or thiazolyl(C_1-C_6)alkyl;

R^5 is carboxy;
C_1-C_6 alkoxycarbonyl; mono- or di- or triphenyl(C_1-C_6)alkoxycarbonyl; benzoyl(C_1-C_6)alkoxycarbonyl; carbamoyl; N- or N,N-di(C_1-C_6)alkylcarbamoyl; C_1-C_6 alkylcarbamoyl substituted by one or two substituents selected from carboxy, C_1-C_6 alkoxycarbonyl, mono or di or triphenyl(C_1-C_6)alkoxycarbonyl and benzoyl(C_1-C_6)alkoxycarbonyl); N-(C_1-C_6)alkyl-N-[carboxy(or C_1-C_6 alkoxycarbonyl)(C_1-

C_6)alkyl]carbamoyl; phenyl(C_1-C_6)alkylcarbamoyl; carboxy- or C_1-C_6 alkoxycarbonyl-substituted phenyl(C_1-C_6)alkylcarbamoyl; C_3-C_7 cycloalkylcarbamoyl; carboxy(C_3-C_7)cycloalkyl(C_1-C_6)alkyl] carbamoyl; C_1-C_6 alkoxycarbonyl (C_3-C_7)cycloalkyl(C_1-C_6)alkyl]c arbamoyl; C_1-C_6 alkylsulfonylcarbamoyl; phenylsulfonylcarbamoyl, carboxy- or C_1-C_6 alkoxycarbonyl-substituted pyridyl(C_1-C_6)alkylcarbamoyl; C_3-C_{10} alkyleneaminocarbonyl; C_3-C_{10} alkyleneaminocarbonyl substituted by carboxy or C_1-C_6 alkoxycarbonyl; [C_3-C_{10} alkyleneamino(C_1-C_6)alkyl]carbamoyl substituted by one to two substituents selected from oxo, carboxy, C_1-C_6 alkoxycarbonyl and carbamoyl; morpholinocarbonyl; morpholinylcarbamoyl; pyridylcarbamoyl; thiazolylcarbamoyl; C_1-C_6 alkylthiadiazolylcarbamoyl; benzothiazolylcarbamoyl; morpholinyl(C_1-C_6)alkylcarbamoyl; pyridyl(C_1-C_6)alkylcarbamoyl; carbazoyl, di(C_1-C_6)alkylcarbazoyl; carboxy(C_1-C_6)alkyl; C_1-C_6 alkoxycarbonyl(C_1-C_6)alkyl; or benzoyl (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl, and

R^6 and R^7 are each hydrogen.

7. The process of Claim 6, wherein

R^1 is N- or N,N-di(C_1-C_{10})alkylcarbamoyl, N-C_1-C_6 alkyl-N-(C_3-C_7)cycloalkylcarbamoyl, N- or N,N-di(C_3-C_7)cycloalkylcarbamoyl, N-(C_1-C_6)alkyl-N-[N,N-di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl]carbamoyl, phenylcarbamoyl, C_3-C_{10} alkyleneaminocarbonyl or N-(C_1-C_6)alkyl-N-[hydroxy(C_1-C_6)alkyl]carbamoyl,

R^2 is C_1-C_6 alkyl,

R^3 is indolyl(C_1-C_6)alkyl, N-(C_1-C_6)alkanoylindolyl(C_1-C_6)alkyl or N-(C_1-C_6)alkylindolyl(C_1-C_6)alkyl,

R^4 is pyridyl(C_1-C_6)alkyl or phenyl(C_1-C_6)alkyl,

R^5 is carboxy, C_1-C_6 alkoxycarbonyl, carbamoyl or N- or N,N-di(C_1-C_6)alkylcarbamoyl, and

A is methylene or -NH-.

8. The process of Claim 7, wherein

R^1 is isopropylcarbamoyl, 2-methylbutylcarbamoyl, heptylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, diisopropylcarbamoyl, dibutylcarbamoyl, diisobutylcarbamoyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, 3,5- or 2,6-dimethylpiperidin-1-ylcarbonyl, hexahydro-1H-azepin-1-ylcarbonyl or octahydroazocin-1-ylcarbonyl,

R^2 is isobutyl,

R^3 is indol-3-ylmethyl, N-formylindol-3-ylmethyl, N-methylindol-3-ylmethyl, N-ethylindol-3-ylmethyl, N-propylindol-3-ylmethyl or N-isobutylindol-3-yl-methyl,

R^4 is 2-pyridylmethyl or benzyl,

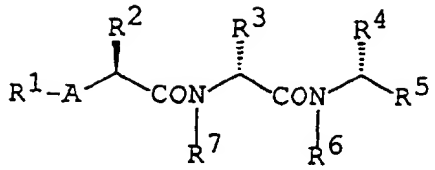
R^5 is carboxy, methoxycarbonyl, ethoxycarbonyl, carbamoyl, methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, N,N-dimethylcarbamoyl or N,N-diethylcarbamoyl.

9. Modification of the process defined in any of claims 1 to 8, additionally comprising admixture or presentation of the compound obtained according to the process of any of claims 1 to 8 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier or excipient.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : DE, AT, GB, FR, BE, IT, NL, CH, LI, LU, SE, DK

1. Peptidverbindung der Formel (I):



(I)

die eine Endothelin-Rezeptor-antagonistische Wirkung besitzt, worin

R^1 Wasserstoff oder Acyl ist,

R^2 $(C_1\text{-}C_6)$Alkyl;

$(C_6\text{-}C_{10})Ar(C_1\text{-}C_6)$alkyl, wahlweise substituiert durch geeignete(n) Substituent(en), ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, $(C_1\text{-}C_6)$Alkoxy, $(C_1\text{-}C_6)$Alkyl, Amino, Nitro und Cyano;
$Cyclo(C_1\text{-}C_6)alkyl(C_1\text{-}C_6)$alkyl; oder
Heterocyclyl$(C_1\text{-}C_6)$alkyl ist, wahlweise substituiert durch geeignete(n) Substituent(en), ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, $(C_1\text{-}C_6)$Alkoxy, $(C_1\text{-}C_6)$Alkyl, Amino, Nitro, Cyano und einer Iminoschutzgruppe;

worin die genannte heterocyclische Gruppe bedeutet:

ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 5 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 Schwefelatom enthalten oder
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,

R^3 Heterocyclyl$(C_1\text{-}C_6)$alkyl oder $(C_6\text{-}C_{10})Ar(C_1\text{-}C_6)$alkyl ist, die jeweils wahlweise mit geeignete(n) Substituent(en) substituiert sind, ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, $(C_1\text{-}C_6)$Alkoxy, $(C_1\text{-}C_6)$Alkyl, Amino, Nitro, Cyano und einer Iminoschutzgruppe,
worin die genannte heterocyclische Gruppe bedeutet:

ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 8- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 5 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e)) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3

Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 Schwefelatom enthalten oder
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,

R^4 $(C_1\text{-}C_6)$Alkyl, $(C_6\text{-}C_{10})Ar(C_1\text{-}C_6)$alkyl, Amino$(C_1\text{-}C_6)$alkyl, geschütztes Amino$(C_1\text{-}C_6)$alkyl, Carboxy$(C_1\text{-}C_6)$alkyl, geschütztes Carboxy$(C_1\text{-}C_6)$alkyl oder wahlweise substituiertes Heterocyclyl$(C_1\text{-}C_6)$alkyl ist,
worin die genannte heterocyclische Gruppe bedeutet:

ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 8- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 5 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 Schwefelatom enthalten, oder
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
worin die genannte heterocyclische Gruppe durch einen oder zwei geeignete(n) Substituent(en) substituiert sein kann, die aus Hydroxy, geschütztem Hydroxy, Halogen, $(C_1\text{-}C_6)$Alkoxy, $(C_1\text{-}C_6)$Alkyl, Amino, Nitro, Cyano und einer Iminoschutzgruppe ausgewählt sind,

R^5 Carboxy, geschütztes Carboxy, Carboxy$(C_1\text{-}C_6)$alkyl oder geschütztes Carboxy$(C_1\text{-}C_6)$alkyl ist,
R^6 Wasserstoff oder wahlweise substituiertes $(C_1\text{-}C_6)$Alkyl ist,
R^7 Wasserstoff oder $(C_1\text{-}C_6)$Alkyl ist, und
A -O-, -NH-, $(C_1\text{-}C_6)$Alkylimino oder $(C_1\text{-}C_6)$Alkylen ist, mit der Maßgabe, daß wenn R^3 Indol-3-ylmethyl oder (N-Formylindol-3-yl)methyl ist, R^2 nicht $(C_3\text{-}C_5)$Alkyl ist,
oder ein pharmazeutisch verträgliches Salz davon.

2. Verbindung nach Anspruch 1, worin

R^3 Heterocyclyl$(C_1\text{-}C_6)$alkyl oder $(C_6\text{-}C_{10})Ar(C_1\text{-}C_6)$alkyl ist, die jeweils wahlweise durch geeignete(n) Substituent(en) substituiert sind, ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, $(C_1\text{-}C_6)$Alkoxy, $(C_1\text{-}C_6)$-Alkyl, Amino, Nitro, Cyano und einer Iminoschutzgruppe, wobei die heterocyclische Gruppe eine ungesättigte kondensierte 8- bis 12-gliedrige heterocyclische Gruppe ist, die 1 bis 5 Stickstoffatom(e) enthält.

3. Verbindung nach Anspruch 2, worin

R^3 9- oder 10-gliedriges benzokondensiertes Heterocyclyl$(C_1\text{-}C_6)$alkyl, worin die heterocyclische Gruppe 1 bis 3 Stickstoffatom(e) enthält und substituiert sein kann durch geeignete(n) Substituent(en), ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, $(C_1\text{-}C_6)$Alkoxy, $(C_1\text{-}C_6)$Alkyl, Amino, Nitro, Cyano und einer Iminoschutzgruppe;
oder $(C_6\text{-}C_{10})Ar(C_1\text{-}C_6)$alkyl ist.

4. Verbindung nach Anspruch 3, worin

R^5 Carboxy, verestertes Carboxy, ausgewählt aus:

$(C_1\text{-}C_6)$Alkoxycarbonyl, $(C_6\text{-}C_{10})Ar(C_1\text{-}C_6)$alkoxycarbonyl und $(C_6\text{-}C_{10})$Aroyl$(C_1\text{-}C_6)$alkoxycarbonyl;
amidiertes Carboxy, ausgewählt aus: Carbamoyl, N- oder N,N-Di$(C_1\text{-}C_6)$alkylcarbamoyl, $(C_1\text{-}C_6)$Alkyl-

carbamoyl substituiert durch 1 oder 2 Substituent(en), ausgewählt aus Carboxy und geschütztem Carboxy, N-(C_1-C_6)Alkyl-N-[Carboxy- oder geschütztes Carboxy(C_1-C_6)alkyl]carbamoyl, (C_6-C_{10})Ar(C_1-C_6)alkylcarbamoyl, Carboxy- oder geschütztes Carboxy-substituiertes (C_6-C_{10})ar(C_1-C_6)alkylcarbamoyl, (C_3-C_7)Cycloalkylcarbamoyl, N-[Carboxy oder geschütztes Carboxy-substituiertes (C_3-C_7)cycloalkyl, (C_1-C_6)alkyl]carbamoyl, (C_1-C_6)Alkylsulfonylcarbamoyl, (C_6-C_{10})Arylsulfonylcarbamoyl, Carboxy- oder geschütztes Carboxy-substituiertes 5- oder 6-gliedriges aromatisches Heteromonocyclyl(C_1-C_6)alkylcarbamoyl, worin der heterocyclische Ring 1 bis 3 Stickstoffatome enthält, (C_3-C_{10})Alkylenaminocarbonyl, (C_3-C_{10})Alkylenaminocarbonyl substituiert durch Carboxy oder geschütztes Carboxy, [(C_3-C_{10})Alkylenamino(C_1-C_6)-alkyl]carbamoyl, substituiert durch 1 oder 2 Substituent(en), ausgewählt aus Oxo, Carboxy, geschütztem Carboxy und Carbamoyl, Morpholinocarbonyl,
5- oder 6-gliedriges gesättigtes Heteromonocyclylcarbamoyl, worin der heterocyclische Ring ein Stickstoffatom und ein Sauerstoffatom enthält,
5- oder 6-gliedriges aromatisches Heteromonocyclylcarbamoyl, worin der heterocyclische Ring 1 bis 3 Stickstoffatome enthält,
5- oder 6-gliedriges aromatisches Heteromonocyclylcarbamoyl, worin der heterocyclische Ring 1 bis 2 Stickstoffatome und 1 Schwefelatom enthält und durch (C_1-C_6)Alkyl substituiert sein kann, 9- oder 10-gliedriges benzokondensiertes Heterocyclylcarbamoyl, worin der heterocyclische Ring 1 oder 2 Stickstoffatome und 1 Schwefelatom enthält, 5- oder 6-gliedriges gesättiges Heteromonocyclyl(C_1-C_6)alkylcarbamoyl, worin der heterocyclische Ring 1 Stickstoffatom und 1 Sauerstoffatom enthält, 5- oder 6-gliedriges aromatisches Heteromonocyclyl(C_1-C_6)Alkylcarbonyl, worin der heterocyclische Ring 1 bis 3 Stickstoffatome enthält, Carbazoyl, Di(C_1-C_6)alkylcarbazoyl;
Carboxy(C_1-C_6)alkyl; oder
geschütztes Carboxy(C_1-C_6)alkyl ist; und

R^6 Wasserstoff oder Heterocyclyl(C_1-C_6)alkyl ist, worin die genannte heterocyclische Gruppe eine ungesättigte 3- bis 8-gliedrige hetermonocyclische Gruppe ist, die 1 bis 4 Stickstoffatom(e) enthält.

5. Verbindung nach Anspruch 4, worin

R^1 Carbamoyl; gesättiges oder ungesättigtes acyclisches oder cyclisches aliphatisches Acyl wahlweise substituiert durch aromatische oder heterocyclische Gruppe(n), aromatisches Acyl, oder heterocyclisches Acyl ist, die sich jeweils von organischen Carbon-, organischen Kohlensäure-, organischen Sulfon- oder organischen Carbaminsäuren ableiten;

R^2 (C_1-C_6)Alkyl; (C_6-C_{10})Ar(C_1-C_6)alkyl; (C_3-C_7)Cycloalkyl(C_1-C_6)alkyl; oder 5- oder 6-gliedriges aromatisches Heteromonocyclyl(C_1-C_6)alkyl ist, worin der heterocyclische Ring 1 bis 3 Stickstoffatome enthält;

R^3 9- oder 10-gliedriges benzokondensiertes Heterocyclyl(C_1-C_6)alkyl ist, worin die heterocyclische Gruppe 1 bis 3 Stickstoffatom(e) enthält und durch (C_1-C_6)Alkyl oder (C_1-C_6)Alkanoyl substituiert sein kann; oder (C_6-C_{10})Ar(C_1-C_6)alkyl ist;

R^4 (C_1-C_6)Alkyl; (C_6-C_{10})Ar(C_1-C_6)alkyl; Amino(C_1-C_6)alkyl; geschütztes Amino(C_1-C_6)alkyl; Carboxy(C_1-C_6)alkyl; geschütztes Carboxy(C_1-C_6)alkyl; 5- oder 6-gliedriges aromatisches Heteromonocyclyl(C_1-C_6)alkyl ist, worin der heterocyclische Ring 1 bis 3 Stickstoffatom(e) enthält; oder 5- oder 6-gliedriges aromatisches Heteromonocyclyl(C_1-C_6)alkyl ist, worin der heterocyclische Ring 1 oder 2 Stickstoffatom(e) und 1 Schwefelatom enthält;

R^5 Carboxy;
verestertes Carboxy, ausgewählt aus:

(C_1-C_6)Alkoxycarbonyl, (C_6-C_{10})Ar(C_1-C_6)alkoxycarbonyl und (C_6-C_{10})Aroyl(C_1-C_6)alkoxycarbonyl;
amidiertes Carboxy ausgewählt aus:
Carbamoyl, N- oder N,N-Di(C_1-C_6)alkylcarbamoyl, (C_1-C_6)Alkylcarbamoyl substituiert durch 1 oder 2 Substituent(en), ausgewählt aus Carboxy und geschütztem Carboxy,
N-(C_1-C_6)Alkyl-N-[Carboxy- oder geschütztes Carboxy(C_1-C_6)alkyl]carbamoyl,
(C_6-C_{10})Ar(C_1-C_6)alkylcarbamoyl,
Carboxy- oder geschütztes Carboxy-substituiertes (C_6-C_{10})ar(C_1-C_6)alkylcarbamoyl,
(C_3-C_7)Cycloalkylcarbamoyl,
N-[Carboxy oder geschütztes Carboxy-substituiertes (C_3-C_7)cycloalkyl, (C_1-C_6)alkyl]carbamoyl,
(C_1-C_6)Alkylsulfonylcarbamoyl, (C_6-C_{10})Arylsulfonylcarbamoyl,
Carboxy- oder geschütztes Carboxy-substituiertes 5- oder 6-gliedriges aromatisches Heteromonocyclyl (C_1-C_6)alkylcarbamoyl, worin der heterocyclische Ring 1 bis 3 Stickstoffatome enthält,

$(C_3$-$C_{10})$Alkylenaminocarbonyl,
$(C_3$-$C_{10})$Alkylenaminocarbonyl substituiert durch Carboxy oder geschütztes Carboxy,
$[(C_3$-$C_{10})$Alkylenamino$(C_1$-$C_6)$alkyl]carbamoyl,
substituiert durch 1 oder 2 Substituent(en), ausgewählt aus Oxo, Carboxy, geschütztem Carboxy und Carbamoyl, Morpholinocarbonyl,
5- oder 6-gliedriges gesättigtes Heteromonocyclylcarbamoyl, worin der heterocyclische Ring ein Stickstoffatom und ein Sauerstoffatom enthält,
5- oder 6-gliedriges aromatisches Heteromonocyclylcarbamoyl, worin der heterocyclische Ring 1 bis 3 Stickstoffatome enthält,
5- oder 6-gliedriges aromatisches Heteromonocyclylcarbamoyl, worin der heterocyclische Ring 1 bis 2 Stickstoffatome und 1 Schwefelatom enthält, und durch $(C_1$-$C_6)$Alkyl substituiert sein kann, 9- oder 10-gliedriges benzokondensiertes Heterocyclylcarbamoyl, worin der heterocyclische Ring 1 oder 2 Stickstoffatome und 1 Schwefelatom enthält, 5- oder 6-gliedriges gesättiges Heteromonocyclyl$(C_1$-$C_6)$alkylcarbamoyl, worin der heterocyclische Ring 1 Stickstoffatom und 1 Sauerstoffatom enthält, 5- oder 6-gliedriges aromatisches Heteromonocyclyl$(C_1$-$C_6)$Alkylcarbonyl, worin der heterocyclische Ring 1 bis 3 Stickstoffatom(e) enthält, Carbazoyl, Di$(C_1$-$C_6)$alkylcarbazoyl;
Carboxy$(C_1$-$C_6)$alkyl; oder
geschütztes $(C_1$-$C_6)$Alkyl ist; und

R^6 Wasserstoff; oder
5- oder 6-gliedriges aromatisches Heteromonocyclyl$(C_1$-$C_6)$alkyl ist, worin der heterocyclische Ring 1 bis 3 Stickstoffatom(e) enthält.

6. Verbindung nach Anspruch 5, worin

R^1 Carbamoyl;

$(C_1$-$C_6)$Alkanoyl;
Amino $(C_1$-$C_6)$alkanoyl;
$(C_1$-$C_6)$Alkoxycarbonyl$(C_1$-$C_6)$alkanoyl;
$(C_3$-$C_7)$Cycloalkylureido$(C_1$-$C_6)$alkanoyl;
$(C_1$-$C_6)$Alkoxycarbonyl;
$(C_3$-$C_7)$Cycloalkyl$(C_1$-$C_6)$alkanoyl;
$(C_3$-$C_7)$Cycloalkylcarbonyl;
$(C_3$-$C_7)$Cycloalkyloxycarbonyl;
Benzoyl; Naphthoyl;
Phenyl$(C_1$-$C_6)$alkanoyl; Naphthyl$(C_1$-$C_6)$alkanoyl;
Amino-substituiertes Phenyl$(C_1$-$C_6)$alkanoyl;
$(C_1$-$C_6)$Alkoxycarbonylamino-substituiertes Phenyl$(C_1$-$C_6)$alkanoyl ist;
Halogenphenyl$(C_1$-$C_6)$alkanoyl;
Phenyl$(C_2$-$C_6)$alkenoyl;
Phenylglyoxyloyl;
Phenyl$(C_1$-$C_6)$alkylphenylglyoxyloyl;
Pyridylcarbonyl;
Tetrahydropyridylcarbonyl;
Tetrahydrochinolylcarbonyl;
Tetrahydroisochinolylcarbonyl;
Morpholinylcarbonyl;
Thiomorpholinylcarbonyl;
Indolylcarbonyl;
Piperazinylcarbonyl, substituiert durch 1 bis 3 Substituenten, ausgewählt aus Oxo und $(C_1$-$C_6)$Alkyl; Pyridyl$(C_1$-$C_6)$alkanoyl;
Morpholinocarbonyl$(C_1$-$C_6)$alkanoyl;
Phenyl$(C_1$-$C_6)$alkylsulfonyl;
N- oder N,N-Di$(C_1$-$C_{10})$alkylcarbamoyl;
Hydroxy$(C_1$-$C_6)$alkylcarbamoyl;
Carboxy$(C_1$-$C_6)$alkylcarbamoyl;
$(C_1$-$C_6)$Alkoxycarbonyl$(C_1$-$C_6)$alkylcarbamoyl;

Carbamoyl(C_1-C_6)alkylcarbamoyl;
[N- oder N,N-Di(C_1-C_6)alkylcarbamoyl](C_1-C_6)-alkylcarbamoyl;
N-(C_1-C_6)Alkyl-N-[hydroxy(C_1-C_6)alkyl]carbamoyl;
N-(C_1-C_6)Alkyl-N-[di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl]carbamoyl;
(C_3-C_{10})Alkylenaminocarbonyl;
Di(C_1-C_6)alkylcarbamoyl(C_3-C_{10})alkylenaminocarbonyl; N-(C_1-C_6)Alkyl-N-(C_3-C_7)cycloalkylcarbamoyl;
Mono- oder Di(C_3-C_7)cycloalkylcarbamoyl;
Hydroxy- oder Di(C_1-C_6)alkylcarbamoyl- oder Di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl-substituiertes (C_3-C_7)Cycloalkylcarbamoyl;
(C_3-C_7)Cycloalkyl(C_1-C_6)alkylcarbamoyl;
Di(C_1-C_6)alkylcarbamoyl-substituiertes (C_3-C_7)Cycloalkyl(C_1-C_6)alkylcarbamoyl;
Di(C_1-C_6)alkylcarbamoyl-substituiertes Phenyl(C_1-C_6)alkylcarbamoyl;
Phenylcarbamoyl, worin die Phenylgruppe substituiert sein kann durch 1 bis 3 Substituent(en), ausgewählt aus Halogen, (C_1-C_6)Alkyl und (C_1-C_6)Alkoxy;
Pyridylcarbamoyl;
N-(C_1-C_6)Alkoxycarbonylpiperidylcarbamoyl;
Morpholinyl(C_1-C_6)alkylcarbamoyl;
(C_1-C_6)Alkanoylcarbazoyl;
(C_3-C_{10})Alkylenaminocarbamoyl;
N-(C_3-C_7)Cycloalkylcarbamoyl(C_1-C_6)alkylcarbamoyl; (C_3-C_{10})Alkylenaminocarbonyl(C_1-C_6)alkylcarbamoyl;
Pyridyl(C_1-C_6)alkylcarbamoyl; oder
Oxo-substituiertes Hexahydroazepinylcarbamoyl;

R^2 (C_1-C_6)Alkyl ist;

R^3 Indolyl (C_1-C_6)alkyl;

N-(C_1-C_6)Alkylindolyl(C_1-C_6)alkyl;
N-(C_1-C_6)Alkanoylindolyl(C_1-C_6)alkyl;
Phenyl(C_1-C_6)alkyl; oder
Naphthyl(C_1-C_6)alkyl ist;

R^4 (C_1-C_6)Alkyl;

Amino(C_1-C_6)alkyl;
Mono- oder Di- oder Triphenyl(C_1-C_6)alkoxycarbonylamino(C_1-C_6)alkyl;
Carboxy(C_1-C_6)alkyl;
Mono- oder Di- oder Triphenyl(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl;
Phenyl(C_1-C_6)alkyl;
Naphthyl(C_1-C_6)alkyl;
Pyridyl(C_1-C_6)alkyl;
Imidazolyl(C_1-C_6)alkyl; oder
Thiazolyl(C_1-C_6)alkyl ist;

R^5 Carboxy;

(C_1-C_6)Alkoxycarbonyl;
Mono- oder Di- oder Triphenyl(C_1-C_6)alkoxycarbonyl; Di(C_1-C_6)alkylcarbamoyl-substituiertes Phenyl(C_1-C_6)alkylcarbamoyl;
Phenylcarbamoyl, worin die Phenylgruppe durch 1 bis 3 Substituenten substituiert sein kann, die aus Halogen, (C_1-C_6)Alkyl und (C_1-C_6)Alkoxy ausgewählt sind;
Pyridylcarbamoyl;
N-(C_1-C_6)Alkoxycarbonylpiperidylcarbamoyl;
Morpholinyl(C_1-C_6)alkylcarbamoyl;
(C_1-C_6)Alkanoylcarbazoyl;
(C_3-C_{10})Alkylenaminocarbamoyl;
N-(C_3-C_7)Cycloalkylcarbamoyl(C_1-C_6)alkylcarbamoyl;
(C_3-C_{10})Alkylenaminocarbonyl(C_1-C_6)alkylcarbamoyl;

Pyridyl(C_1-C_6)alkylcarbamoyl; oder Oxo-substituiertes Hexahydroazepinylcarbamoyl ist;

R^2 (C_1-C_6)Alkyl ist;

R^3 Indolyl (C_1-C_6)alkyl;

N-(C_1-C_6)Alkylindolyl(C_1-C_6)alkyl;
N-(C_1-C_6)Alkanoylindolyl(C_1-C_6)alkyl;
Phenyl(C_1-C_6)alkyl; oder
Naphthyl(C_1-C_6)alkyl ist;

R^4 (C_1-C_6)Alkyl;

Amino (C_1-C_6)alkyl;
Mono- oder Di- oder Triphenyl(C_1-C_6)alkoxycarbonylamino(C_1-C_6)alkyl;
Carboxy(C_1-C_6)alkyl;
Mono- oder Di- oder Triphenyl(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl;
Phenyl(C_1-C_6)alkyl;
Naphthyl(C_1-C_6)alkyl;
Pyridyl(C_1-C_6)alkyl;
Imidazolyl(C_1-C_6)alkyl oder
Thiazolyl(C_1-C_6)alkyl ist;

R^5 Carboxy;

(C_1-C_6)Alkoxycarbonyl;
Mono- oder Di- oder Triphenyl(C_1-C_6)alkoxycarbonyl; Benzoyl(C_1-C_6)alkoxycarbonyl;
Carbamoyl;
N- oder N,N-Di(C_1-C_6)alkylcarbamoyl;
(C_1-C_6)Alkylcarbamoyl, substituiert durch 1 oder 2
Substituenten ausgewählt aus Carboxy, (C_1-C_6)Alkoxycarbonyl, Mono- oder Di- oder Triphenyl(C_1-C_6) alkoxycarbonyl und Benzoyl(C_1-C_6)alkoxycarbonyl);
N-(C_1-C_6)Alkyl-N-[carboxy(oder(C_1-C_6)alkoxycarbonyl)
(C_1-C_6)alkyl]carbamoyl;
Phenyl(C_1-C_6)alkylcarbamoyl;
Carboxy- oder (C_1-C_6)Alkkoxycarbonyl-substituiertes Phenyl(C_1-C_6)alkylcarbamoyl;
(C_3-C_7)Cycloalkylcarbamoyl;
Carboxy(C_3-C_7)cycloalkyl(C_1-C_6)alkyl]carbamoyl;
(C_1-C_6)Alkoxycarbonyl(C_3-C_7)cycloalkyl(C_1-C_6)alkyl]carbamoyl;
(C_1-C_6)Alkylsulfonylcarbamoyl;
Phenylsulfonylcarbamoyl, Carboxy- oder (C_1-C_6)Alkoxycarbonyl-substituiertes Pyridyl(C_1-C_6)alkylcarbamoyl;
(C_3-C_{10})Alkylenaminocarbonyl;
(C_3-C_{10})Alkylenaminocarbonyl, substituiert durch Carboxy oder (C_1-C_6)Alkoxycarbonyl;
[(C_3-C_{10})Alkylenamino(C_1-C_6)alkyl]carbamoyl, substituiert durch ein bis zwei Substituenten ausgewählt aus Oxo, Carboxy, (C_1-C_6)Alkoxycarbonyl und Carbamoyl;
Morpholinocarbonyl;
Morpholinylcarbamoyl;
Pyridylcarbamoyl;
Thiazolylcarbamoyl;
(C_1-C_6)Alkylthiadiazolylcarbamoyl;
Benzothiazolylcarbamoyl;
Morpholinyl(C_1-C_6)alkylcarbamoyl;
Pyridyl(C_1-C_6)alkylcarbamoyl;
Carbazoyl,
Di(C_1-C_6)alkylcarbazoyl;
Carboxy(C_1-C_6)alkyl;
(C_1-C_6)Alkoxycarbonyl(C_1-C_6)alkyl; oder
Benzoyl(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl ist, und

R^6 und R^7 jeweils Wasserstoff sind.

7. Verbindung nach Anspruch 6, worin

R^1 N- oder N,N-Di(C_1-C_{10})alkylcarbamoyl, N-(C_1-C_6)Alkyl-N-(C_3-C_7)cycloalkylcarbamoyl, N- oder N,N-Di(C_3-C_7)cycloalkylcarbamoyl, N-(C_1-C_6)Alkyl-N-[N,N-di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl]carbamoyl, Phenylcarbamoyl, (C_3-C_{10})Alkylenaminocarbonyl oder N-(C_1-C_6)Alkyl-N-[hydroxy(C_1-C_6)alkyl]carbamoyl ist,
R^2 (C_1-C_6)Alkyl ist,
R^3 Indolyl (C_1-C_6)alkyl, N-(C_1-C_6)Alkanoylindolyl(C_1-C_6)alkyl oder N-(C_1-C_6)-Alkylindolyl(C_1-C_6)alkyl ist,
R^4 Pyridyl(C_1-C_6)alkyl oder Phenyl(C_1-C_6)alkyl ist,
R^5 Carboxy,

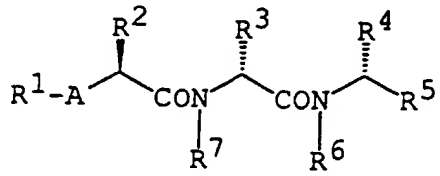
(C_1-C_6)Alkoxycarbonyl,
Carbamoyl oder
N- oder N,N-Di(C_1-C_6)alkylcarbamoyl ist, und

A Methylen oder -NH- ist.

8. Verbindung nach Anspruch 7, worin

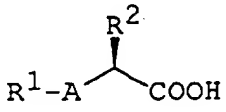
R^1 Isopropylcarbamoyl, 2-Methylbutylcarbamoyl, Heptylcarbamoyl, Dimethylcarbamoyl, Diethylcarbamoyl, Dipropylcarbvamoyl, Diisopropylcarbamoyl, Dibutylcarbamoyl, Diisobutylcarbamoyl, Pyrrolidin-1-ylcarbonyl, Piperidin-1-ylcarbonyl, 3,5- oder 2,6-dimethylpiperidin-1-ylcarbonyl, Hexahydro-1H-azepin-1-ylcarbonyl oder Octahydroazocin-1-ylcarbonyl ist,
R^2 Isobutyl ist,
R^3 Indol-3-ylmethyl, N-Formylindo-3-ylmethyl, N-Methylindol-3-ylmethyl, N-Ethylindol-3-ylmethyl, N-Propylindol-3-ylmethyl oder N-Isobutylindol-3-ylmethyl ist,
R^4 2-Pyridylmethyl oder Benzyl ist,
R^5 Carboxy, Methoxycarbonyl, Ethoxycarbonyl, Carbamoyl, Methylcarbamoyl, Ethylcarbamoyl, Propylcarbamoyl, Isopropylcarbamoyl, Butylcarbamoyl, N,N-Dimethylcarbamoyl oder N,N-Diethylcarbamoyl ist.

9. Verfahren zur Herstellung einer Peptidverbindung der Formel (I):



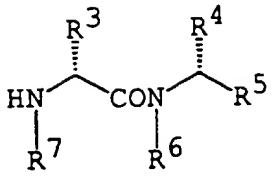
worin R^1, R^2, R^3, R^4, R^5, R^6 R^7 und A wie im Anspruch 1 definiert sind,
oder Salzen davon, das umfaßt:

(a) Reagieren einer Verbindung der Formel:



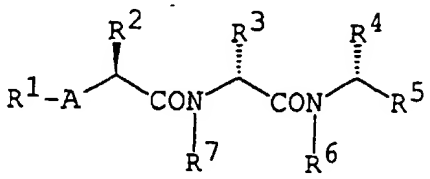
(II)

worin R^1, R^2 und A wie oben definiert sind, oder eines reaktiven Derivates an der Carboxygruppe oder eines Salzes davon mit einer Verbindung der Formel:



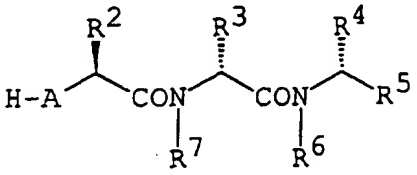
(III)

worin R^3, R^4, R^5, R^6 und R^7 jeweils wie oben definiert sind, oder deren reaktives Derivat an der Aminogruppe oder einem Salz davon, um eine Verbindung der Formel:



(I)

worin R^1, R^2, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind, oder ein Salz davon zu ergeben; oder
(b) Reagieren einer Verbindung der Formel:

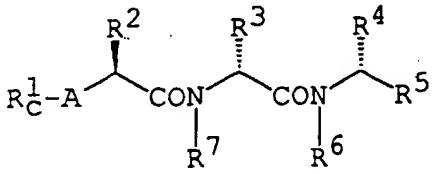


(I-a)

worin R^2, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind, oder deren reaktives Derivat an der Aminogruppe oder eines Salzes davon mit einer Verbindung der Formel:

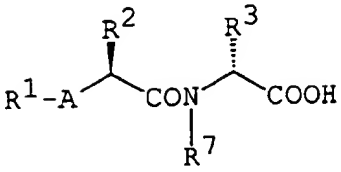
$$R^1_c\text{-OH} \qquad \text{(IV)}$$

worin $R^1{}_c$ Acyl ist,
oder deren reaktives Derivat an der Carboxygruppe oder einem Salz davon, um eine Verbindung der Formel:



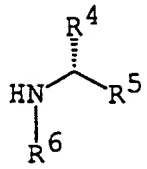
(I-b)

worin R^1, R^2, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind, oder ein Salz davon zu ergeben; oder
(c) Reagieren einer Verbindung der Formel:



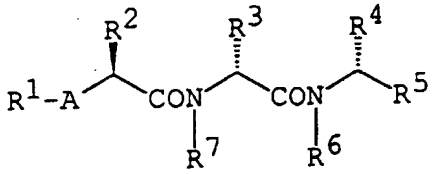
(V)

worin R^1, R^2, R^3, R^7 und A jeweils wie oben definiert sind, oder eines reaktiven Derivates an der Carboxygruppe oder eines Salzes davon mit einer Verbindung der Formel:



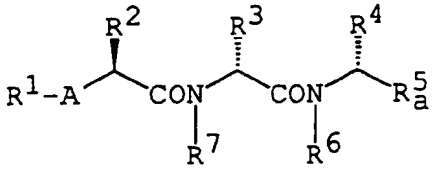
(VI)

worin R^4, R^5, und R^6 jeweils wie oben definiert sind, oder einem reaktiven Derivat an der Aminogruppe, oder einem Salz davon, um eine Verbindung der Formel zu ergeben:



(I)

worin R^1, R^2, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind, oder ein Salz davon zu ergeben; oder (d) Unterwerfen einer Verbindung der Formel:

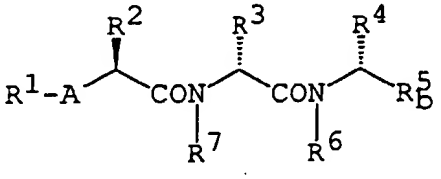


(I-c)

worin R^1, R^2, R^3, R^4, R^6, R^7 und A jeweils wie oben definiert sind und

R^5_a geschütztes Carboxy oder geschütztes Carboxy(C_1-C_6)alkyl ist,

oder eines Salzes davon der Entfernungsreaktion der Carboxyschutzgruppe, um eine Verbindung der Formel:

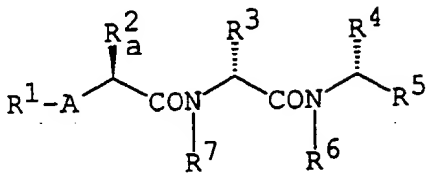


(I-d)

zu ergeben, worin R^1, R^2, R^3, R^4, R^6, R^7 und A jeweils wie oben definiert sind und

$R^5{}_b$ Carboxy oder Carboxy(C_1-C_6)alkyl ist

oder ein Salz davon zu ergeben; oder
(e) Unterwerfen einer Verbindung der Formel:



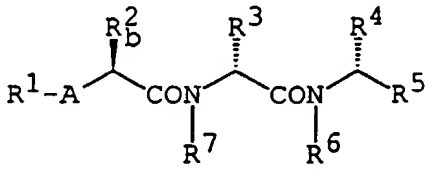
(I-e)

worin R^1, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind und

$R^2{}_a$ geschütztes Imino ist, das Heterocyclyl(C_1-C_6)alkyl, wahlweise substituiert durch geeignete(n) Substituent(en), ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, (C_1-C_6)Alkoxy, (C_1-C_6)Alkyl, Amino, Nitro und Cyano, enthält;
worin die genannte heterocyclische Gruppe bedeutet:

ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 5 Stickstoffatom (e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Sauerstoffatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten, oder
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Schwefelatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,

oder einem Salz davon, der Entfernungsreaktion der Imino-Schutzgruppe in $R^2{}_a$, um eine Verbindung der Formel:



(I-f)

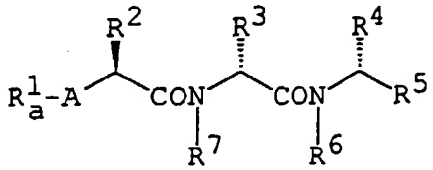
worin R^1, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind und

$R^2{}_b$ Imino ist, das Heterocyclyl(C_1-C_6)alkyl, wahlweise substituiert durch geeignete Substituent(en), ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, (C_1-C_6)Alkoxy, (C_1-C_6)Alkyl, Amino, Nitro und Cyano enthält;
worin die genannte heterocyclische Gruppe bedeutet:

ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,

gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 5 Stickstoffatom (e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Sauerstoffatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten, oder
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Schwefelatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,

oder ein Salz davon; oder
(f) Unterwerfen einer Verbindung der Formel:

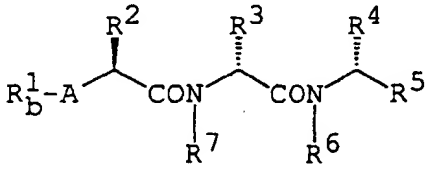


(I-g)

worin R^2, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind und

$R^1{}_a$ Acyl, substituiert durch eine geschütztes Aminogruppe ist,

oder eines Salzes davon, der Entfernungsreaktion der Aminoschutzgruppe, um eine Verbindung der Formel:

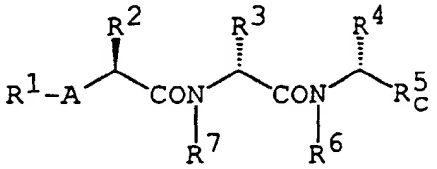


(I-h)

worin R^2, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind und

$R^1{}_b$ Acyl, substituiert durch eine Aminogruppe ist, oder ein Salz davon zu ergeben; oder

(g) Umsetzen einer Verbindung der Formel:

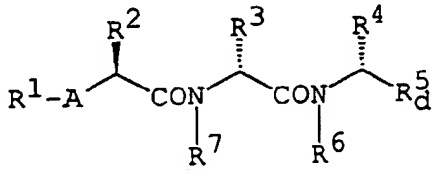


(I-i)

worin R^1, R^2, R^3, R^4, R^6, R^7 und A jeweils wie oben definiert sind und

$R^5{}_c$ verestertes Carboxy wie in Anspruch 4 definiert ist,

oder deren reaktives Derivat an der Carboxygruppe oder eines Salzes davon mit einem wahlweise substituierten Amin oder einem Salz davon, um eine Verbindung der Formel:

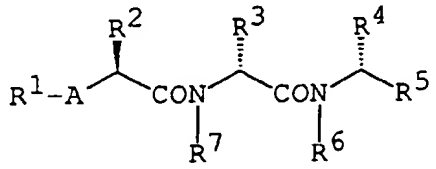


(I-j)

worin R^1, R^2, R^3, R^4, R^6, R^7 und A jeweils wie oben definiert sind und

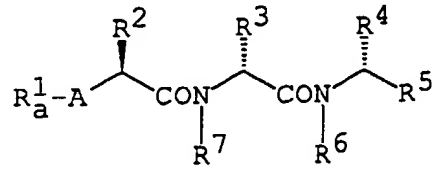
$R^5{}_d$ amidiertes Carboxy ist, wie in Anspruch 4 definiert,

oder ein Salz davon zu ergeben; oder
(h) Acylieren der Aminogruppe in $R^1{}_b$ der Verbindung der Formel:



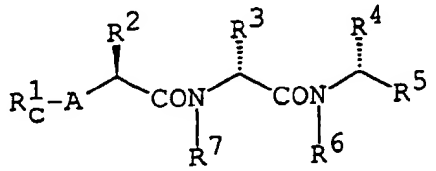
(I-h)

worin $R^1{}_b$, R^2, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind,
oder eines Salzes davon, um eine Verbindung der Formel:



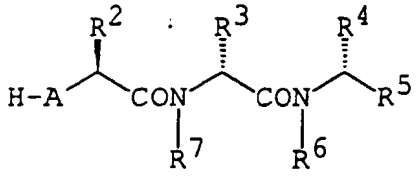
(I-g)

worin $R^1{}_a$, R^2, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind,
oder ein Salz davon zu ergeben; oder
(i) Unterwerfen einer Verbindung der Formel:



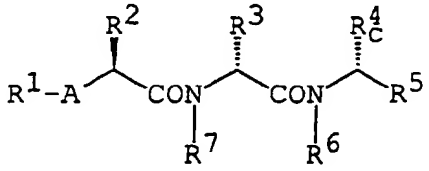
(I-b)

worin $R^1{}_c$, R^2, R^3, R^4, R^6, R^7 und A jeweils wie oben definiert sind,
oder eines Salzes davon, der Entfernungsreaktion der Acylgruppe von $R^1{}_c$, um eine Verbindung der Formel:



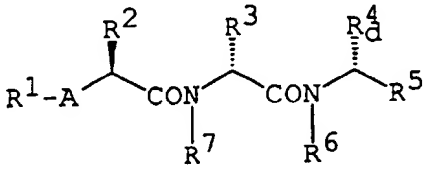
(I-a)

worin R^2, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind,
oder ein Salz davon zu ergeben; oder
(j) Unterwerfen einer Verbindung der Formel:



(I-k)

worin R^1, R^2, R^3, R^5, R^6, R^7 und A jeweils wie oben definiert sind und
$R^4{}_c$ geschütztes Carboxy(C_1-C_6)alkyl ist, oder eines Salzes davon, der Entfernungsreaktion der Carboxyschutzgruppe in $R^4{}_c$, um eine Verbindung der Formel:

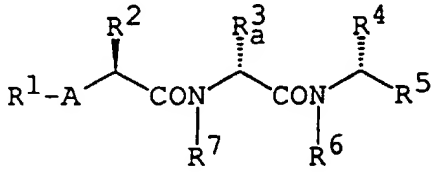


(I-l)

worin R^1, R^2, R^3, R^5, R^6, R^7 und A jeweils wie oben definiert sind und

$R^4{}_d$ Carboxy(C_1-C_6)alkyl ist,

oder ein Salz davon zu ergeben; oder
(k) Unterwerfen einer Verbindung der Formel:



(I-m)

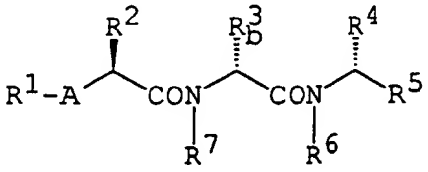
worin R^1, R^2, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind und

$R^3{}_a$ geschütztes Imino ist, das Heterocyclyl(C_1-C_6)alkyl, wahlweise substituiert durch geeignete Substituent(en), ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, (C_1-C_6)Alkoxy, (C_1-C_6)Alkyl, Amino, Nitro und Cyano enthält;
worin die genannte heterocyclische Gruppe bedeutet:

ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 5 Stickstoffatom

(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Sauerstoffatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten, oder
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Schwefelatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,

oder eines Salzes davon, der Entfernungsreaktion der Iminoschutzgruppe in R^3_a, um eine Verbindung der Formel:



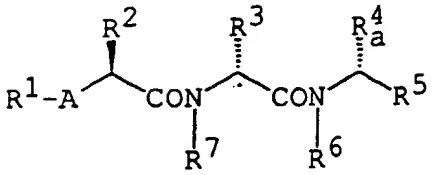
(I-n)

worin R^1, R^2, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind, und

R^3_b Imino ist, das Heterocyclyl(C_1-C_6)alkyl, wahlweise substituiert durch geeignete Substituent(en), ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, (C_1-C_6)Alkoxy, (C_1-C_6)Alkyl, Amino, Nitro und Cyano enthält;
worin die genannte heterocyclische Gruppe bedeutet:

ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 5 Stickstoffatom (e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Sauerstoffatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten, oder
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Schwefelatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,

oder ein Salz davon zu ergeben; oder
(1) Unterwerfen einer Verbindung der Formel:



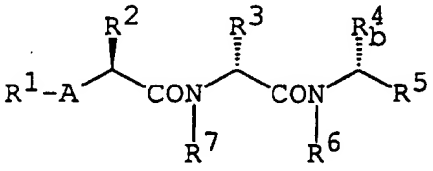
(I-o)

worin R^1, R^2, R^3, R^5, R^6, R^7 und A jeweils wie oben definiert sind, und

R^4_a geschütztes Amino(C_1-C_6)alkyl oder geschütztes Imino, das Heterocyclyl(C_1-C_6)alkyl enthält, ist, worin die genannte heterocyclische Gruppe bedeutet:

ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 5 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten, oder
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,

worin die genannte heterocyclische Gruppe durch einen oder zwei geeignete(n) Substituent(en), ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, (C_1-C_6)Alkoxy, (C_1-C_6)Alkyl, Amino, Nitro und Cyano, substituiert sein kann,
oder eines Salzes davon, der Entfernungsreaktion der Amino- oder Imino-Schutzgruppe in R^4_a, um eine Verbindung der Formel:



(I-p)

worin R^1, R^2, R^3, R^5, R^6, R^7 und A jeweils wie oben definiert sind, und

R^4_b Amino(C_1-C_6)alkyl oder Imino ist, das Heterocyclyl(C_1-C_6)alkyl enthält, worin die genannte heterocyclische Gruppe bedeutet:

ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 5 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,

gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Sauerstoffatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten, oder
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Schwefelatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,

worin die genannte heterocyclische Gruppe durch einen oder zwei geeignete(n) Substituent(en), ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, (C_1-C_6)Alkoxy, (C_1-C_6)Alkyl, Amino, Nitro und Cyano, substituiert sein kann,

oder ein Salz davon zu ergeben.

10. Pharmazeutische Zusammensetzung, die eine Verbindung nach Anspruch 1 oder ein pharmazeutisch verträgliches Salz davon und einen pharmazeutisch verträglichen Träger oder Exzipienten umfaßt.

11. Verfahren für die Herstellung einer pharmazeutischen Zusammensetzung, das das Mischen der Verbindung nach Anspruch 1 oder eines pharmazeutisch verträglichen Salzes davon mit einem pharmazeutisch verträglichen Träger oder Exzipienten umfaßt.

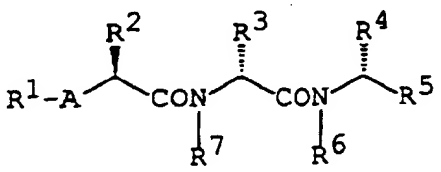
12. Verbindung nach Anspruch 1 oder pharmazeutisch verträgliche Salze davon für die Verwendung als Medikament.

13. Verbindung nach Anspruch 1 oder pharmazeutisch verträgliche Salze davon für die Verwendung als endothelinantagonistisches Mittel.

14. Verwendung der Verbindung nach Anspruch 1 oder pharmazeutisch verträglicher Salze davon für die Herstellung eines Medikamentes für die Behandlung von Endothelinvermittelten Erkrankungen.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung von Peptidverbindung der Formel (I):



(I)

die eine Endothelin-Rezeptor-antagonistische Wirkung besitzt, worin

R^1 Wasserstoff oder Acyl ist,
R^2 (C_1-C_6)Alkyl;

(C_6-C_{10})Ar(C_1-C_6)alkyl, wahlweise substituiert durch geeignete(n) Substituent(en), ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, (C_1-C_6)Alkoxy, (C_1-C_6)Alkyl, Amino, Nitro und Cyano;
Cyclo(C_1-C_6)alkyl(C_1-C_6)alkyl; oder
Heterocyclyl(C_1-C_6)alkyl ist, wahlweise substituiert durch geeignete(n) Substituent(en), ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, (C_1-C_6)Alkoxy, (C_1-C_6)Alkyl, Amino, Nitro, Cyano und einer Iminoschutzgruppe;

worin die genannte heterocyclische Gruppe bedeutet:

ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 5 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 Schwefelatom enthalten oder
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,

R^3 Heterocyclyl(C_1-C_6)alkyl oder
(C_6-C_{10})Ar(C_1-C_6)alkyl ist, die jeweils wahlweise mit geeignete(n) Substituent(en) substituiert sind, ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, (C_1-C_6)Alkoxy, (C_1-C_6)Alkyl, Amino, Nitro, Cyano und einer Iminoschutzgruppe,
worin die genannte heterocyclische Gruppe bedeutet:

ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 8- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 5 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 Schwefelatom enthalten oder
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,

R^4 (C_1-C_6)Alkyl, (C_6-C_{10})Ar(C_1-C_6)alkyl, Amino(C_1-C_6)alkyl, geschütztes Amino(C_1-C_6)alkyl, Carboxy(C_1-C_6)alkyl, geschütztes Carboxy(C_1-C_6)alkyl oder wahlweise substituiertes Heterocyclyl(C_1-C_6)alkyl ist,
worin die genannte heterocyclische Gruppe bedeutet:

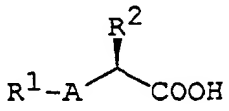
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 8- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 5 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,

gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 Schwefelatom enthalten, oder
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
worin die genannte heterocyclische Gruppe durch einen oder zwei geeignete(n) Substituent(en) substituiert sein kann, die aus Hydroxy, geschütztem Hydroxy, Halogen, (C_1-C_6)Alkoxy, (C_1-C_6)Alkyl, Amino, Nitro, Cyano und einer Iminoschutzgruppe ausgewählt sind,

R^5 Carboxy, geschütztes Carboxy, Carboxy(C_1-C_6)alkyl oder geschütztes Carboxy(C_1-C_6)alkyl ist,
R^6 Wasserstoff oder wahlweise substituiertes (C_1-C_6)Alkyl ist,
R^7 Wasserstoff oder (C_1-C_6)Alkyl ist, und
A -O-, -NH-, (C_1-C_6)Alkylimino oder (C_1-C_6)Alkylen ist, mit der Maßgabe, daß wenn R^3 Indol-3-ylmethyl oder (N-Formylindol-3-yl)methyl ist, R^2 nicht (C_3-C_5)Alkyl ist,

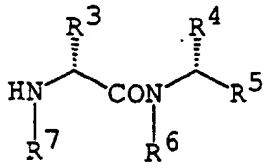
oder eines pharmazeutisch verträglichen Salzes davon das umfaßt:

(a) Reagieren einer Verbindung der Formel:



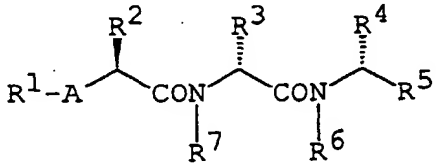
(II)

worin R^1, R^2 und A wie oben definiert sind, oder eines reaktiven Derivates an der Carboxygruppe oder eines Salzes davon mit einer Verbindung der Formel:



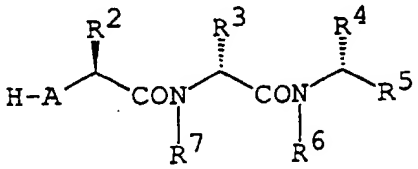
(III)

worin R^3, R^4, R^5, R^6 und R^7 jeweils wie oben definiert sind, oder deren reaktives Derivat an der Aminogruppe oder einem Salz davon, um eine Verbindung der Formel:



(I)

worin R^1, R^2, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind, oder ein Salz davon zu ergeben; oder
(b) Reagieren einer Verbindung der Formel:

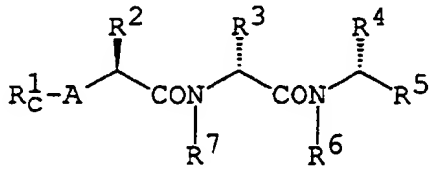


(I-a)

worin R^2, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind, oder deren reaktives Derivat an der Aminogruppe oder eines Salzes davon mit einer Verbindung der Formel:

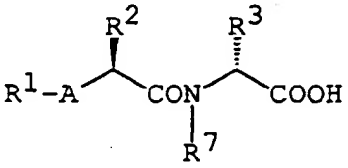
$$R^1{}_c\text{-OH} \qquad \text{(IV)}$$

worin $R^1{}_c$ Acyl ist,
oder deren reaktives Derivat an der Carboxygruppe oder einem Salz davon, um eine Verbindung der Formel:



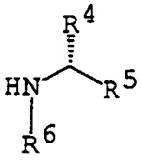
(I-b)

worin R^1, R^2, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind, oder ein Salz davon zu ergeben; oder
(c) Reagieren einer Verbindung der Formel:



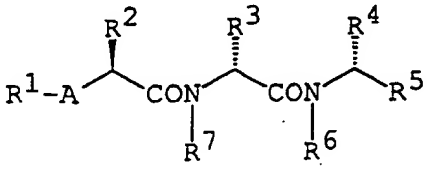
(V)

worin R^1, R^2, R^3, R^7 und A jeweils wie oben definiert sind, oder eines reaktiven Derivates an der Carboxygruppe oder eines Salzes davon mit einer Verbindung der Formel:



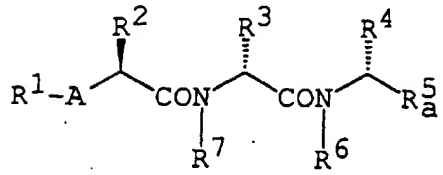
(VI)

worin R^4, R^5, und R^6 jeweils wie oben definiert sind, oder einem reaktiven Derivat an der Aminogruppe, oder einem Salz davon, um eine Verbindung der Formel zu ergeben:



(I)

worin R^1, R^2, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind, oder ein Salz davon zu ergeben; oder
(d) Unterwerfen einer Verbindung der Formel:

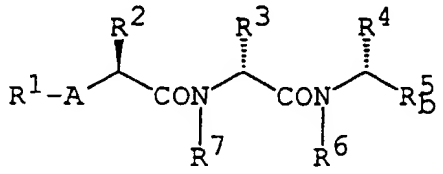


(I-c)

worin R^1, R^2, R^3, R^4, R^6, R^7 und A jeweils wie oben definiert sind und

$R^5{}_a$ geschütztes Carboxy oder geschütztes Carboxy(C_1-C_6)alkyl ist,

oder eines Salzes davon der Entfernungsreaktion der Carboxyschutzgruppe, um eine Verbindung der Formel:

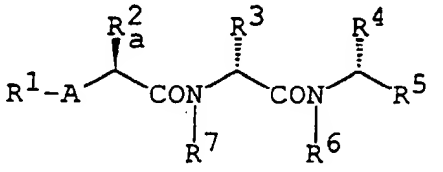


(I-d)

zu ergeben, worin R^1, R^2, R^3, R^4, R^6, R^7 und A jeweils wie oben definiert sind und

$R^5{}_b$ Carboxy oder Carboxy(C_1-C_6)alkyl ist

oder ein Salz davon zu ergeben; oder
(e) Unterwerfen einer Verbindung der Formel:



(I-e)

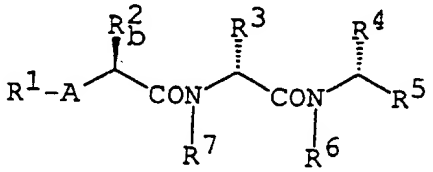
worin R^1, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind und

$R^2{}_a$ geschütztes Imino ist, das Heterocyclyl(C_1-C_6)alkyl, wahlweise substituiert durch geeignete (n) Substituent(en), ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, (C_1-C_6)Alkoxy, (C_1-C_6)Alkyl, Amino, Nitro und Cyano, enthält;
worin die genannte heterocyclische Gruppe bedeutet:

ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 5 Stickstoffatom (e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Sauerstoffatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis

3 Stickstoffatom(e) enthalten, oder
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Schwefelatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,

oder einem Salz davon, der Entfernungsreaktion der Imino-Schutzgruppe in R^{2}_{a}, um eine Verbindung der Formel:



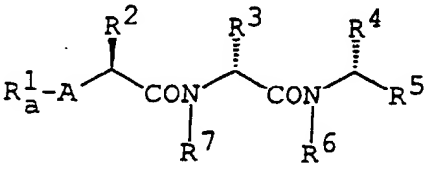
(I-f)

worin R^1, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind und

R^{2}_{b} Imino ist, das Heterocyclyl(C_1-C_6)alkyl, wahlweise substituiert durch geeignete Substituent(en), ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, (C_1-C_6)Alkoxy, (C_1-C_6)Alkyl, Amino, Nitro und Cyano enthält;
worin die genannte heterocyclische Gruppe bedeutet:

ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 5 Stickstoffatom (e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Sauerstoffatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten, oder
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Schwefelatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,

oder ein Salz davon; oder
(f) Unterwerfen einer Verbindung der Formel:

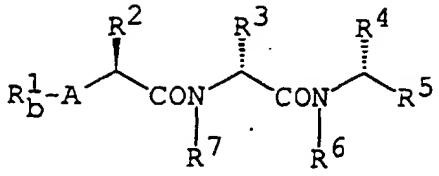


(I-g)

worin R^2, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind und

R^{1}_{a} Acyl, substituiert durch eine geschütztes Aminogruppe ist,

oder eines Salzes davon, der Entfernungsreaktion der Aminoschutzgruppe, um eine Verbindung der Formel:

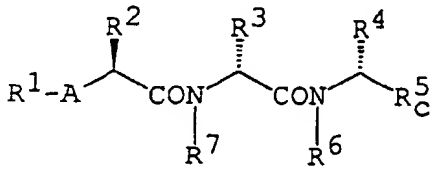


(I-h)

worin R^2, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind und

$R^1{}_b$ Acyl, substituiert durch eine Aminogruppe ist, oder ein Salz davon zu ergeben; oder

(g) Umsetzen einer Verbindung der Formel:

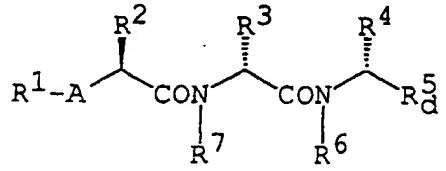


(I-i)

worin R^1, R^2, R^3, R^4, R^6, R^7 und A jeweils wie oben definiert sind und

$R^5{}_c$ verestertes Carboxy wie in Anspruch 4 definiert ist,

oder deren reaktives Derivat an der Carboxygruppe oder eines Salzes davon mit einem wahlweise substituierten Amin oder einem Salz davon, um eine Verbindung der Formel:

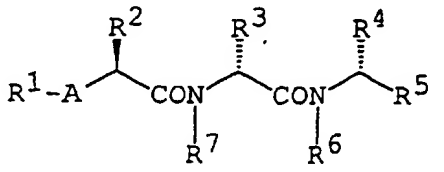


(I-j)

worin R^1, R^2, R^3, R^4, R^6, R^7 und A jeweils wie oben definiert sind und

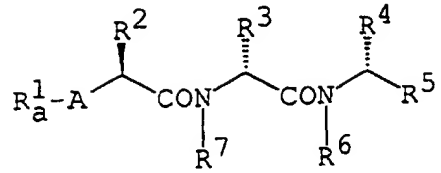
$R^5{}_d$ amidiertes Carboxy ist, wie in Anspruch 4 definiert,

oder ein Salz davon zu ergeben; oder
(h) Acylieren der Aminogruppe in $R^1{}_b$ der Verbindung der Formel:



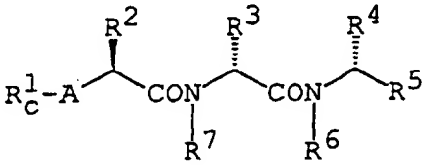
(I-h)

worin $R^1{}_b$, R^2, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind,
oder eines Salzes davon, um eine Verbindung der Formel:



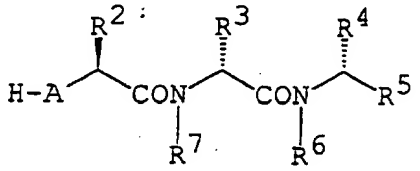
(I-g)

worin R^1_a, R^2, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind,
oder ein Salz davon zu ergeben; oder
(i) Unterwerfen einer Verbindung der Formel:



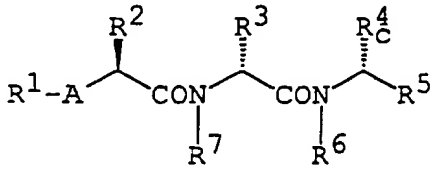
(I-b)

worin R^1_c, R^2, R^3, R^4, R^6 R^7 und A jeweils wie oben definiert sind,
oder eines Salzes davon, der Entfernungsreaktion der Acylgruppe von R^1_c, um eine Verbindung der Formel:



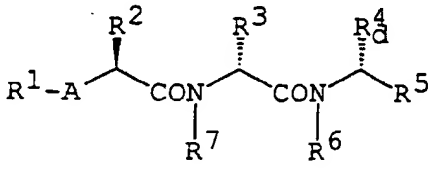
(I-a)

worin R^2, R^3, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind,
oder ein Salz davon zu ergeben; oder
(j) Unterwerfen einer Verbindung der Formel:



(I-k)

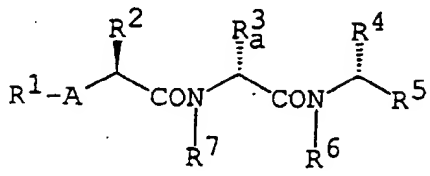
worin R^1, R^2, R^3, R^5, R^6, R^7 und A jeweils wie oben definiert sind und
R^4_c geschütztes Carboxy(C_1-C_6)alkyl ist, oder eines Salzes davon, der Entfernungsreaktion der Carboxyschutzgruppe in R^4_c, um eine Verbindung der Formel:



(I-l)

worin R^1, R^2, R^3, R^5, R^6, R^7 und A jeweils wie oben definiert sind und
R^4_d Carboxy(C_1-C_6)alkyl ist, oder ein Salz davon zu ergeben; oder

(k) Unterwerfen einer Verbindung der Formel:



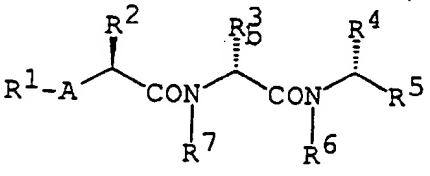
(I-m)

worin R^1, R^2, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind und

R^3_a geschütztes Imino ist, das Heterocyclyl(C_1-C_6)alkyl, wahlweise substituiert durch geeignete Substituent(en), ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, (C_1-C_6)Alkoxy, (C_1-C_6)Alkyl, Amino, Nitro und Cyano enthält;
worin die genannte heterocyclische Gruppe bedeutet:

ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 5 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten, oder
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,

oder eines Salzes davon, der Entfernungsreaktion der Iminoschutzgruppe in R^3_a, um eine Verbindung der Formel:



(I-n)

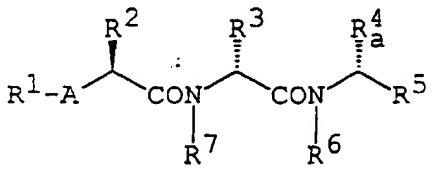
worin R^1, R^2, R^4, R^5, R^6, R^7 und A jeweils wie oben definiert sind, und

R^3_b Imino ist, das Heterocyclyl(C_1-C_6)alkyl, wahlweise substituiert durch geeignete Substituent(en), ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, (C_1-C_6)Alkoxy, (C_1-C_6)Alkyl, Amino, Nitro und Cyano enthält;
worin die genannte heterocyclische Gruppe bedeutet:

ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 5 Stickstoffatom

(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Sauerstoffatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten, oder
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Schwefelatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,

oder ein Salz davon zu ergeben; oder
(I) Unterwerfen einer Verbindung der Formel:



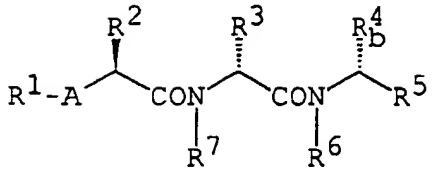
(I-o)

worin R^1, R^2, R^3, R^5, R^6, R^7 und A jeweils wie oben definiert sind, und

$R^4{}_a$ geschütztes Amino(C_1-C_6)alkyl oder geschütztes Imino, das Heterocyclyl(C_1-C_6)alkyl enthält, ist, worin die genannte heterocyclische Gruppe bedeutet:

ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 5 Stickstoffatom (e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Sauerstoffatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten, oder
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Schwefelatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,
worin die genannte heterocyclische Gruppe durch einen oder zwei geeignete(n) Substituent(en), ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, (C_1-C_6)Alkoxy, (C_1-C_6)Alkyl, Amino, Nitro und Cyano, substituiert sein kann,

oder eines Salzes davon, der Entfernungsreaktion der Amino- oder Imino-Schutzgruppe in $R^4{}_a$, um eine Verbindung der Formel:



(I-p)

worin R^1, R^2, R^3, R^5, R^6, R^7 und A jeweils wie oben definiert sind, und

$R^4{}_b$ Amino(C_1-C_6)alkyl oder Imino ist, das Heterocyclyl(C_1-C_6)alkyl enthält, worin die genannte heterocyclische Gruppe bedeutet:

ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 4 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 5 Stickstoffatom (e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Sauerstoffatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Sauerstoffatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,
ungesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten,
gesättigte 3- bis 8-gliedrige heteromonocyclische Gruppen, die 1 bis 2 Schwefelatom(e) und 1 bis 3 Stickstoffatom(e) enthalten, oder
ungesättigte kondensierte 7- bis 12-gliedrige heterocyclische Gruppen, die 1 bis 2 Schwefelatom (e) und 1 bis 3 Stickstoffatom(e) enthalten,
worin die genannte heterocyclische Gruppe durch einen oder zwei geeignete(n) Substituent(en), ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, (C_1-C_6)Alkoxy, (C_1-C_6)Alkyl, Amino, Nitro und Cyano, substituiert sein kann,

oder ein Salz davon zu ergeben.

2. Verfahren nach Anspruch 1, worin

R^3 Heterocyclyl(C_1-C_6)alkyl oder (C_6-C_{10})Ar(C_1-C_6)alkyl ist, die jeweils wahlweise durch geeignete(n) Substituent(en) substituiert sind, ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, (C_1-C_6)Alkoxy, (C_1-C_6)Alkyl, Amino, Nitro, Cyano und einer Iminoschutzgruppe, wobei die heterocyclische Gruppe eine ungesättigte kondensierte 8- bis 12-gliedrige heterocyclische Gruppe ist, die 1 bis 5 Stickstoffatom(e) enthält.

3. Verfahren nach Anspruch 2, worin

R^3 9- oder 10-gliedriges benzokondensiertes Heterocyclyl(C_1-C_6)alkyl, worin die heterocyclische Gruppe 1 bis 3 Stickstoffatom(e) enthält und substituiert sein kann durch geeignete(n) Substituent(en), ausgewählt aus Hydroxy, geschütztem Hydroxy, Halogen, (C_1-C_6)Alkoxy, (C_1-C_6)Alkyl, Amino, Nitro, Cyano und einer Iminoschutzgruppe;
oder (C_6-C_{10})Ar(C_1-C_6)alkyl ist.

4. Verfahren nach Anspruch 3, worin

R^5 Carboxy, verestertes Carboxy, ausgewählt aus:

(C_1-C_6)Alkoxycarbonyl, (C_6-C_{10})Ar(C_1-C_6)alkoxycarbonyl und (C_6-C_{10})Aroyl(C_1-C_6)alkoxycarbonyl; amidiertes Carboxy, ausgewählt aus: Carbamoyl,
N- oder N,N-Di(C_1-C_6)alkylcarbamoyl, (C_1-C_6)Alkylcarbamoyl substituiert durch 1 oder 2 Substituent(en),

ausgewählt aus Carboxy und geschütztem Carboxy,
N-(C_1-C_6)Alkyl-N-[Carboxy- oder geschütztes Carboxy(C_1-C_6)alkyl]carbamoyl,
(C_6-C_{10})Ar(C_1-C_6)alkylcarbamoyl,
Carboxy- oder geschütztes Carboxy-substituiertes (C_6-C_{10})ar(C_1-C_6)alkylcarbamoyl,
(C_3-C_7)Cycloalkylcarbamoyl,
N-[Carboxy oder geschütztes Carboxy-substituiertes (C_3-C_7)cycloalkyl, (C_1-C_6)alkyl]carbamoyl,
(C_1-C_6)Alkylsulfonylcarbamoyl, (C_6-C_{10})Arylsulfonylcarbamoyl,
Carboxy- oder geschütztes Carboxy-substituiertes 5- oder 6-gliedriges aromatisches Heteromonocyclyl (C_1-C_6)alkylcarbamoyl, worin der heterocyclische Ring 1 bis 3 Stickstoffatome enthält,
(C_3-C_{10})Alkylenaminocarbonyl,
(C_3-C_{10})Alkylenaminocarbonyl substituiert durch Carboxy oder geschütztes Carboxy,
[(C_3-C_{10})Alkylenamino(C_1-C_6)-alkyl]carbamoyl, substituiert durch 1 oder 2 Substituent(en), ausgewählt aus Oxo, Carboxy, geschütztem Carboxy und Carbamoyl, Morpholinocarbonyl,
5- oder 6-gliedriges gesättigtes Heteromonocyclylcarbamoyl, worin der heterocyclische Ring ein Stickstoffatom und ein Sauerstoffatom enthält,
5- oder 6-gliedriges aromatisches Heteromonocyclylcarbamoyl, worin der heterocyclische Ring 1 bis 3 Stickstoffatome enthält,
5- oder 6-gliedriges aromatisches Heteromonocyclylcarbamoyl, worin der heterocyclische Ring 1 bis 2 Stickstoffatome und 1 Schwefelatom enthält und durch (C_1-C_6)Alkyl substituiert sein kann, 9- oder 10-gliedriges benzokondensiertes Heterocyclylcarbamoyl, worin der heterocyclische Ring 1 oder 2 Stickstoffatome und 1 Schwefelatom enthält, 5- oder 6-gliedriges gesättiges Heteromonocyclyl(C_1-C_6)alkylcarbamoyl, worin der heterocyclische Ring 1 Stickstoffatom und 1 Sauerstoffatom enthält, 5- oder 6-gliedriges aromatisches Heteromonocyclyl(C_1-C_6)Alkylcarbonyl, worin der heterocyclische Ring 1 bis 3 Stickstoffatome enthält, Carbazoyl, Di(C_1-C_6)alkylcarbazoyl;
Carboxy(C_1-C_6)alkyl; oder
geschütztes Carboxy(C_1-C_6)alkyl ist; und

R^6 Wasserstoff oder Heterocyclyl(C_1-C_6)alkyl ist, worin die genannte heterocyclische Gruppe eine ungesättigte 3- bis 8-gliedrige hetermonocyclische Gruppe ist, die 1 bis 4 Stickstoffatom(e) enthält.

5. Verfahren nach Anspruch 4, worin

R^1 Carbamoyl; gesättiges oder ungesättigtes acyclisches oder cyclisches aliphatisches Acyl wahlweise substituiert durch aromatische oder heterocyclische Gruppe(n), aromatisches Acyl, oder heterocyclisches Acyl ist, die sich jeweils von organischen Carbon-, organischen Kohlensäure-, organischen Sulfon- oder organischen Carbaminsäuren ableiten;

R^2 (C_1-C_6)Alkyl; (C_6-C_{10})Ar(C_1-C_6)alkyl; (C_3-C_7)Cycloalkyl(C_1-C_6)alkyl; oder 5- oder 6-gliedriges aromatisches Heteromonocyclyl(C_1-C_6)alkyl ist, worin der heterocyclische Ring 1 bis 3 Stickstoffatome enthält;

R^3 9- oder 10-gliedriges benzokondensiertes Heterocyclyl(C_1-C_6)alkyl ist, worin die heterocyclische Gruppe 1 bis 3 Stickstoffatom(e) enthält und durch (C_1-C_6)Alkyl oder (C_1-C_6)Alkanoyl substituiert sein kann; oder (C_6-C_{10})Ar(C_1-C_6)alkyl ist;

R^4 (C_1-C_6)Alkyl; (C_6-C_{10})Ar(C_1-C_6)alkyl; Amino(C_1-C_6)alkyl; geschütztes Amino(C_1-C_6)alkyl; Carboxy(C_1-C_6)alkyl; geschütztes Carboxy(C_1-C_6)alkyl; 5- oder 6-gliedriges aromatisches Heteromonocyclyl(C_1-C_6)alkyl ist, worin der heterocyclische Ring 1 bis 3 Stickstoffatom(e) enthält; oder 5- oder 6-gliedriges aromatisches Heteromonocyclyl(C_1-C_6)alkyl ist, worin der heterocyclische Ring 1 oder 2 Stickstoffatom(e) und 1 Schwefelatom enthält;

R^5 Carboxy;
verestertes Carboxy, ausgewählt aus:

(C_1-C_6)Alkoxycarbonyl, (C_6-C_{10})Ar(C_1-C_6)alkoxycarbonyl und (C_6-C_{10})Aroyl(C_1-C_6)alkoxycarbonyl;
amidiertes Carboxy ausgewählt aus:
Carbamoyl, N- oder N,N-Di(C_1-C_6)alkylcarbamoyl, (C_1-C_6)Alkylcarbamoyl substituiert durch 1 oder 2 Substituent(en), ausgewählt aus Carboxy und geschütztem Carboxy,
N-(C_1-C_6)Alkyl-N-[Carboxy- oder geschütztes Carboxy(C_1-C_6)alkyl]carbamoyl,
(C_6-C_{10})Ar(C_1-C_6)alkylcarbamoyl,
Carboxy- oder geschütztes Carboxy-substituiertes (C_6-C_{10})ar(C_1-C_6)alkylcarbamoyl,
(C_3-C_7)Cycloalkylcarbamoyl, N-[Carboxy oder geschütztes Carboxy-substituiertes (C_3-C_7)cycloalkyl, (C_1-C_6)alkyl]carbamoyl,

(C_1-C_6)Alkylsulfonylcarbamoyl, (C_6-C_{10})Arylsulfonylcarbamoyl,
Carboxy- oder geschütztes Carboxy-substituiertes 5- oder 6-gliedriges aromatisches Heteromonocyclyl (C_1-C_6)alkylcarbamoyl, worin der heterocyclische Ring 1 bis 3 Stickstoffatome enthält,
(C_3-C_{10})Alkylenaminocarbonyl,
(C_3-C_{10})Alkylenaminocarbonyl substituiert durch Carboxy oder geschütztes Carboxy,
[(C_3-C_{10})Alkylenamino (C_1-C_6)alkyl]carbamoyl,
substituiert durch 1 oder 2 Substituent(en), ausgewählt aus Oxo, Carboxy, geschütztem Carboxy und Carbamoyl, Morpholinocarbonyl,
5- oder 6-gliedriges gesättigtes Heteromonocyclylcarbamoyl, worin der heterocyclische Ring ein Stickstoffatom und ein Sauerstoffatom enthält,
5- oder 6-gliedriges aromatisches Heteromonocyclylcarbamoyl, worin der heterocyclische Ring 1 bis 3 Stickstoffatome enthält,
5- oder 6-gliedriges aromatisches Heteromonocyclylcarbamoyl, worin der heterocyclische Ring 1 bis 2 Stickstoffatome und 1 Schwefelatom enthält, und durch (C_1-C_6)Alkyl substituiert sein kann, 9- oder 10-gliedriges benzokondensiertes Heterocyclylcarbamoyl, worin der heterocyclische Ring 1 oder 2 Stickstoffatome und 1 Schwefelatom enthält, 5- oder 6-gliedriges gesättiges Heteromonocyclyl(C_1-C_6)alkylcarbamoyl, worin der heterocyclische Ring 1 Stickstoffatom und 1 Sauerstoffatom enthält, 5- oder 6-gliedriges aromatisches Heteromonocyclyl(C_1-C_6)Alkylcarbonyl, worin der heterocyclische Ring 1 bis 3 Stickstoffatom(e) enthält, Carbazoyl, Di(C_1-C_6)alkylcarbazoyl;
Carboxy(C_1-C_6)alkyl; oder
geschütztes (C_1-C_6)Alkyl ist; und

R^6 Wasserstoff; oder
5- oder 6-gliedriges aromatisches Heteromonocyclyl(C_1-C_6)alkyl ist, worin der heterocyclische Ring 1 bis 3 Stickstoffatom(e) enthält.

6. Verfahren nach Anspruch 5, worin

R^1 Carbamoyl;

(C_1-C_6)Alkanoyl;
Amino (C_1-C_6)alkanoyl;
(C_1-C_6)Alkoxycarbonyl(C_1-C_6)alkanoyl;
(C_3-C_7)Cycloalkylureido(C_1-C_6)alkanoyl;
(C_1-C_6)Alkoxycarbonyl;
(C_3-C_7)Cycloalkyl (C_1-C_6)alkanoyl;
(C_3-C_7)Cycloalkylcarbonyl;
(C_3-C_7)Cycloalkyloxycarbonyl;
Benzoyl; Naphthoyl;
Phenyl(C_1-C_6)alkanoyl; Naphthyl(C_1-C_6)alkanoyl;
Amino-substituiertes Phenyl(C_1-C_6) alkanoyl;
(C_1-C_6)Alkoxycarbonylamino-substituiertes Phenyl(C_1-C_6)alkanoyl ist;
Halogenphenyl(C_1-C_6)alkanoyl;
Phenyl(C_2-C_6)alkenoyl;
Phenylglyoxyloyl;
Phenyl(C_1-C_6)alkylphenylglyoxyloyl;
Pyridylcarbonyl;
Tetrahydropyridylcarbonyl;
Tetrahydrochinolylcarbonyl;
Tetrahydroisochinolylcarbonyl;
Morpholinylcarbonyl;
Thiomorpholinylcarbonyl;
Indolylcarbonyl;
Piperazinylcarbonyl, substituiert durch 1 bis 3 Substituenten, ausgewählt aus Oxo und (C_1-C_6)Alkyl; Pyridyl(C_1-C_6)alkanoyl;
Morpholinocarbonyl(C_1-C_6)alkanoyl;
Phenyl(C_1-C_6)alkylsulfonyl;
N- oder N,N-Di(C_1-C_{10})alkylcarbamoyl;

Hydroxy(C_1-C_6)alkylcarbamoyl;
Carboxy(C_1-C_6)alkylcarbamoyl;
(C_1-C_6)Alkoxycarbonyl(C_1-C_6)alkylcarbamoyl;
Carbamoyl(C_1-C_6)alkylcarbamoyl;
[N- oder N,N-Di(C_1-C_6)alkylcarbamoyl](C_1-C_6)alkylcarbamoyl;
N-(C_1-C_6)Alkyl-N-[hydroxy(C_1-C_6)alkyl]carbamoyl;
N-(C_1-C_6)Alkyl-N-[di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl]carbamoyl;
(C_3-C_{10})Alkylenaminocarbonyl;
Di(C_1-C_6)alkylcarbamoyl(C_3-C_{10})alkylenaminocarbonyl; N-(C_1-C_6)Alkyl-N-(C_3-C_7)cycloalkylcarbamoyl;
Mono- oder Di(C_3-C_7)cycloalkylcarbamoyl;
Hydroxy- oder Di(C_1-C_6)alkylcarbamoyl- oder Di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl-substituiertes (C_3-C_7)Cycloalkylcarbamoyl;
(C_3-C_7)Cycloalkyl(C_1-C_6)alkylcarbamoyl;
Di(C_1-C_6)alkylcarbamoyl-substituiertes (C_3-C_7)Cycloalkyl(C_1-C_6)alkylcarbamoyl;
Di(C_1-C_6)alkylcarbamoyl-substituiertes Phenyl(C_1-C_6)alkylcarbamoyl;
Phenylcarbamoyl, worin die Phenylgruppe substituiert sein kann durch 1 bis 3 Substituent(en), ausgewählt aus Halogen, (C_1-C_6)Alkyl und (C_1-C_6)Alkoxy;
Pyridylcarbamoyl;
N-(C_1-C_6)Alkoxycarbonylpiperidylcarbamoyl;
Morpholinyl(C_1-C_6)alkylcarbamoyl;
(C_1-C_6)Alkanoylcarbazoyl;
(C_3-C_{10})Alkylenaminocarbamoyl;
N-(C_3-C_7)Cycloalkylcarbamoyl(C_1-C_6)alkylcarbamoyl;
(C_3-C_{10})Alkylenaminocarbonyl(C_1-C_6)alkylcarbamoyl;
Pyridyl(C_1-C_6)alkylcarbamoyl; oder
Oxo-substituiertes Hexahydroazepinylcarbamoyl;

R^2 (C_1-C_6)Alkyl ist;
R^3 Indolyl (C_1-C_6)alkyl;

N-(C_1-C_6)Alkylindolyl(C_1-C_6)alkyl;
N-(C_1-C_6)Alkanoylindolyl(C_1-C_6)alkyl;
Phenyl(C_1-C_6)alkyl; oder
Naphthyl(C_1-C_6)alkyl ist;

R^4 (C_1-C_6)Alkyl;

Amino(C_1-C_6)alkyl;
Mono- oder Di- oder Triphenyl(C_1-C_6)alkoxycarbonylamino(C_1-C_6)alkyl;
Carboxy(C_1-C_6)alkyl;
Mono- oder Di- oder Triphenyl(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl;
Phenyl(C_1-C_6)alkyl;
Naphthyl(C_1-C_6)alkyl;
Pyridyl(C_1-C_6)alkyl;
Imidazolyl(C_1-C_6)alkyl; oder
Thiazolyl(C_1-C_6)alkyl ist;

R^5 Carboxy;

(C_1-C_6)Alkoxycarbonyl;
Mono- oder Di- oder Triphenyl(C_1-C_6)alkoxycarbonyl; Di(C_1-C_6)alkylcarbamoyl-substituiertes Phenyl(C_1-C_6)alkylcarbamoyl;
Phenylcarbamoyl, worin die Phenylgruppe durch 1 bis 3 Substituenten substituiert sein kann, die aus Halogen, (C_1-C_6)Alkyl und (C_1-C_6)Alkoxy ausgewählt sind;
Pyridylcarbamoyl;
N-(C_1-C_6)Alkoxycarbonylpiperidylcarbamoyl;
Morpholinyl(C_1-C_6)alkylcarbamoyl;
(C_1-C_6)Alkanoylcarbazoyl;

(C_3-C_{10})Alkylenaminocarbamoyl;
N-(C_3-C_7)Cycloalkylcarbamoyl(C_1-C_6)alkylcarbamoyl;
(C_3-C_{10})Alkylenaminocarbonyl(C_1-C_6)alkylcarbamoyl;
Pyridyl(C_1-C_6)alkylcarbamoyl; oder
Oxo-substituiertes Hexahydroazepinylcarbamoyl ist;

R^2 (C_1-C_6)Alkyl ist;
R^3 Indolyl(C_1-C_6)alkyl;

N-(C_1-C_6)Alkylindolyl(C_1-C_6)alkyl;
N-(C_1-C_6)Alkanoylindolyl(C_1-C_6)alkyl;
Phenyl(C_1-C_6)alkyl; oder
Naphthyl(C_1-C_6)alkyl ist;

R^4 (C_1-C_6)Alkyl;

Amino(C_1-C_6)alkyl;
Mono- oder Di- oder Triphenyl(C_1-C_6)alkoxycarbonylamino(C_1-C_6)alkyl;
Carboxy(C_1-C_6)alkyl;
Mono- oder Di- oder Triphenyl(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl;
Phenyl(C_1-C_6)alkyl;
Naphthyl(C_1-C_6)alkyl;
Pyridyl(C_1-C_6)alkyl;
Imidazolyl(C_1-C_6)alkyl oder
Thiazolyl(C_1-C_6)alkyl ist;

R^5 Carboxy;

(C_1-C_6)Alkoxycarbonyl;
Mono- oder Di- oder Triphenyl(C_1-C_6)alkoxycarbonyl; Benzoyl(C_1-C_6)alkoxycarbonyl;
Carbamoyl;
N- oder N,N-Di(C_1-C_6)alkylcarbamoyl;
(C_1-C_6)Alkylcarbamoyl, substituiert durch 1 oder 2 Substituenten ausgewählt aus Carboxy, (C_1-C_6)Alkoxycarbonyl, Mono- oder Di- oder Triphenyl(C_1-C_6)alkoxycarbonyl und Benzoyl(C_1-C_6)alkoxycarbonyl);
N-(C_1-C_6)Alkyl-N-[carboxy(oder(C_1-C_6)alkoxycarbonyl) (C_1-C_6)alkyl]carbamoyl;
Phenyl(C_1-C_6)alkylcarbamoyl;
Carboxy- oder (C_1-C_6)Alkkoxycarbonyl-substituiertes Phenyl(C_1-C_6)alkylcarbamoyl;
(C_3-C_7)Cycloalkylcarbamoyl;
Carboxy(C_3-C_7)cycloalkyl(C_1-C_6)alkyl]carbamoyl;
(C_1-C_6)Alkoxycarbonyl(C_3-C_7)cycloalkyl(C_1-C_6)alkyl]carbamoyl;
(C_1-C_6)Alkylsulfonylcarbamoyl;
Phenylsulfonylcarbamoyl,
Carboxy- oder (C_1-C_6)Alkoxycarbonyl-substituiertes Pyridyl(C_1-C_6)alkylcarbamoyl;
(C_3-C_{10})Alkylenaminocarbonyl;
(C_3-C_{10})Alkylenaminocarbonyl, substituiert durch Carboxy oder (C_1-C_6)Alkoxycarbonyl;
[(C_3-C_{10})Alkylenamino(C_1-C_6)alkyl]carbamoyl, substituiert durch ein bis zwei Substituenten ausgewählt aus Oxo, Carboxy, (C_1-C_6)Alkoxycarbonyl und Carbamoyl;
Morpholinocarbonyl;
Morpholinylcarbamoyl;
Pyridylcarbamoyl;
Thiazolylcarbamoyl;
(C_1-C_6)Alkylthiadiazolylcarbamoyl;
Benzothiazolylcarbamoyl;
Morpholinyl(C_1-C_6)alkylcarbamoyl;
Pyridyl(C_1-C_6)alkylcarbamoyl;
Carbazoyl,
Di(C_1-C_6)alkylcarbazoyl;
Carboxy(C_1-C_6) alkyl;

(C_1-C_6)Alkoxycarbonyl(C_1-C_6)alkyl; oder
Benzoyl(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl ist, und

R^6 und R^7 jeweils Wasserstoff sind.

7. Verfahren nach Anspruch 6, worin

R^1 N- oder N,N-Di(C_1-C_{10})alkylcarbamoyl, N-(C_1-C_6)Alkyl-N-(C_3-C_7)cycloalkylcarbamoyl, N- oder N,N-Di(C_3-C_7)cycloalkylcarbamoyl, N-(C_1-C_6)Alkyl-N-[N,N-di(C_1-C_6)alkylcarbamoyl(C_1-C_6)alkyl]carbamoyl, Phenylcarbamoyl, (C_3-C_{10})Alkylenaminocarbonyl oder N-(C_1-C_6)Alkyl-N-[hydroxy(C_1-C_6)alkyl]carbamoyl ist,
R^2 (C_1-C_6)Alkyl ist,
R^3 Indolyl (C_1-C_6)alkyl, N-(C_1-C_6)Alkanoylindolyl(C_1-C_6)alkyl oder N-(C_1-C_6)Alkylindolyl(C_1-C_6)alkyl ist,
R^4 Pyridyl(C_1-C_6)alkyl oder Phenyl(C_1-C_6)alkyl ist,
R^5 Carboxy,

(C_1-C_6)Alkoxycarbonyl,
Carbamoyl oder
N- oder N,N-Di(C_1-C_6)alkylcarbamoyl ist, und

A Methylen oder -NH- ist.

8. Verfahren nach Anspruch 7, worin

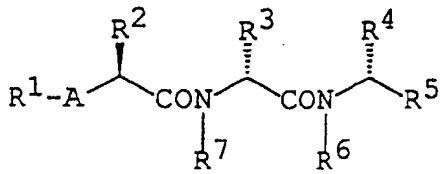
R^1 Isopropylcarbamoyl, 2-Methylbutylcarbamoyl, Heptylcarbamoyl, Dimethylcarbamoyl, Diethylcarbamoyl, Dipropylcarbvamoyl, Diisopropylcarbamoyl, Dibutylcarbamoyl, Diisobutylcarbamoyl, Pyrrolidin-1-ylcarbonyl, Piperidin-1-ylcarbonyl, 3,5- oder 2,6-dimethylpiperidin-1-ylcarbonyl, Hexahydro-1H-azepin-1-ylcarbonyl oder Octahydroazocin-1-ylcarbonyl ist,
R^2 Isobutyl ist,
R^3 Indol-3-ylmethyl, N-Formylindo-3-ylmethyl, N-Methylindol-3-ylmethyl, N-Ethylindol-3-ylmethyl, N-Propylindol-3-ylmethyl oder N-Isobutylindol-3-ylmethyl ist,
R^4 2-Pyridylmethyl oder Benzyl ist,
R^5 Carboxy, Methoxycarbonyl, Ethoxycarbonyl, Carbamoyl, Methylcarbamoyl, Ethylcarbamoyl, Propylcarbamoyl, Isopropylcarbamoyl, Butylcarbamoyl, N,N-Dimethylcarbamoyl oder N,N-Diethylcarbamoyl ist.

9. Modifizierung des Verfahrens, definiert in irgendeinem der Ansprüche 1 bis 8, das zusätzlich das Mischen oder die Präsentation der Verbindung, die in dem Verfahren nach irgendeinem der Ansprüche 1 bis 8 erhalten wurde, oder eines pharmazeutisch verträglichen Salzes davon mit pharmazeutisch verträglichen Trägern oder Exzipienten umfaßt.

Revendications

Revendications pour les Etats contractants suivants : DE, AT, GB, FR, BE, IT, NL, CH, LI, LU, SE, DK

1. Composé de type peptide de formule (I) :



(I)

ayant une activité antagoniste des récepteurs de l'endothéline,
formule dans laquelle :

R^1 représente un atome d'hydrogène ou un groupe acyle,

R^2 représente un groupe alkyle en C_1-C_6;
un groupe (ar en C_6-C_{10})(alkyle en C_1-C_6) facultativement substitué par un ou plusieurs substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6; un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro et un groupe cyano; un groupe cyclo(alkyl en C_1-C_6) (alkyle en C_1-C_6); ou un groupe (groupe hétérocyclique)(alkyle en C_1-C_6) facultativement substitué par un ou plusieurs substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6; un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro, un groupe cyano et un groupe protecteur du groupe imino; ledit groupe hétérocyclique étant

un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 5 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome (s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant un atome de soufre, ou
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,

R^3 représente un groupe (groupe hétérocyclique)(alkyle en C_1-C_6) ou
un groupe (ar en C_6-C_{10})(alkyle en C_1-C_6), chacun facultativement substitué par un ou plusieurs substituant (s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6; un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro, un groupe cyano et un groupe protecteur du groupe imino, ledit groupe hétérocyclique étant

un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 8 à 12 chaînons contenant 1 à 5 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) d'oxygène et à 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome (s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant un atome de soufre, ou
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,

R^4 représente un groupe alkyle en C_1-C_6, un groupe (ar en C_6-C_{10})(alkyle en C_1-C_6), un groupe amino(alkyle en C_1-C_6), un groupe (amino protégé)(alkyle en C_1-C_6), un groupe carboxy(alkyle en C_1-C_6), un groupe (carboxy protégé)(alkyle en C_1-C_6) ou un groupe (groupe hétérocyclique)(alkyle en C_1-C_6) facultativement substitué,
ledit groupe hétérocyclique étant

un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,

un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 8 à 12 chaînons contenant 1 à 5 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome (s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant un atome de soufre, ou
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,

sachant que ledit groupe hétérocyclique peut être substitué par un ou deux substituants(s) approprié(s) choisi (s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6, un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro, un groupe cyano et un groupe protecteur du groupe imino,

R^5 représente un groupe carboxy, un groupe carboxy protégé, un groupe carboxy(alkyle en C_1-C_6), ou un groupe (carboxy protégé)(alkyle en C_1-C_6),

R^6 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_6 facultativement substitué,

R^7 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_6, et

A représente -O-, -NH-, un groupe (alkyl en C_1-C_6)imino ou un groupe alkylène en C_1-C_6, sous réserve que lorsque R^3 représente un groupe indol-3-ylméthyle ou un groupe (N-formylindol-3-yl)méthyle, alors R^2 ne représente pas un groupe alkyle en C_3-C_5,

ou un sel pharmaceutiquement acceptable de ce composé.

2. Composé selon la revendication 1, dans lequel :

R^3 représente un groupe (groupe hétérocyclique) (alkyle en C_1-C_6) ou un groupe (ar en C_6-C_{10})(alkyle en C_1-C_6), chacun facultativement substitué par un ou plusieurs substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6; un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro, un groupe cyano et un groupe protecteur du groupe imino, ledit groupe hétérocyclique étant
un groupe hétérocyclique insaturé condensé à 8 à 12 chaînons contenant 1 à 5 atome(s) d'azote.

3. Composé selon la revendication 2, dans lequel :

R^3 représente un groupe (groupe hétérocyclique condensé au benzène à 9 ou 10 chaînons) (alkyle en C_1-C_6), dans lequel le groupe hétérocyclique contient un à trois atome(s) d'azote et peut être substitué par un ou plusieurs substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6, un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro, un groupe cyano et un groupe protecteur du groupe imino;
ou un groupe (ar en C_6-C_{10})(alkyle en C_1-C_6).

4. Composé selon la revendication 3, dans lequel

R^5 représente un groupe carboxy, un groupe carboxy estérifié choisi parmi :

un groupe (alcoxy en C_1-C_6)carbonyle,
un groupe (ar en C_6-C_{10})(alcoxy en C_1-C_6)carbonyle, et un groupe (aroyl en C_6-C_{10})(alcoxy en C_1-C_6) carbonyle;
un groupe carboxy amidé, choisi parmi :
un groupe carbamoyle,
un groupe N- ou N,N-di(alkyl en C_1-C_6)carbamoyle,

un groupe (alkyl en C_1-C_6) carbamoyle substitué par un ou deux substituant(s) choisi(s) parmi un groupe carboxy et un groupe carboxy protégé,
un groupe N-(alkyl en C_1-C_6)-N-[carboxy- ou (carboxy protégé)(alkyl en C_1-C_6)]carbamoyle,
un groupe (ar en C_6-C_{10})(alkyl en C_1-C_6)carbamoyle,
un groupe (ar en C_6-C_{10})(alkyl en C_1-C_6)carbamoyle substitué par un groupe carboxy ou carboxy protégé,
un groupe (cycloalkyl en C_3-C_7)carbamoyle,
Un groupe N-[(cycloalkyl en C_3-C_7)(alkyl en C_1-C_6) substitué par un groupe carboxy ou carboxy protégé] carbamoyle,
un groupe (alkyl en C_1-C_6)sulfonylcarbamoyle, un groupe (aryl en C_6-C_{10})sulfonylcarbamoyle,
un groupe [(groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)(groupe alkyl en C_1-C_6) substitué par un groupe carboxy ou un groupe carboxy protégé]carbamoyle dans lequel l'hétérocyclique contient un à trois atome(s) d'azote,
un groupe (alkylène en C_3-C_{10})aminocarbonyle,
un groupe (alkylène en C_3-C_{10})aminocarbonyle substitué par un groupe carboxy ou un groupe carboxy protégé,
un groupe [(alkylène en C_3-C_{10})amino(alkyl en C_1-C_6)]carbamoyle substitué par un ou deux substituant (s) choisi(s) parmi un groupe oxo, un groupe carboxy, un groupe carboxy protégé et un groupe carbamoyle,
un groupe morpholinocarbonyle,
un groupe (groupe hétéromonocyclique saturé à 5 ou 6 chaînons)carbamoyle, dans lequel l'hétérocyclique contient un atome d'azote et un atome d'oxygène,
un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)carbamoyle, dans lequel l'hétérocyclique contient 1 à 3 atomes d'azote,
un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)carbamoyle, dans lequel l'hétérocycle contient 1 à 2 atome(s) d'azote et un atome de soufre et peut être substitué par un groupe alkyle en C_1-C_6, un groupe (groupe hétérocyclique condensé au benzène à 9 ou 10 chaînons)carbamoyle, dans lequel l'hétérocyclique contient un à deux atome(s) d'azote et un atome de soufre, un groupe (groupe hétéromonocyclique saturé à 5 ou 6 chaînons)(alkyl en C_1-C_6)carbamoyle, dans lequel l'hétérocyclique contient un atome d'azote et un atome d'oxygène, un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons) (alkyl en C_1-C_6)carbonyle, dans lequel l'hétérocycle contient 1 à 3 atome(s) d'azote, un groupe carbazoyle, un groupe di(alkyl en C_1-C_6)carbazoyle;
un groupe carboxy(alkyle en C_1-C_6); ou
un groupe (carboxy protégé)(alkyle en C_1-C_6); et

R^6 représente un atome d'hydrogène ou un groupe (groupe hétérocyclique)(alkyle en C_1-C_6), dans lequel ledit groupe hétérocyclique est un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome (s) d'azote.

5. Composé selon la revendication 4, dans laquelle :

R^1 représente un groupe carbamoyle; un groupe acyle aliphatique, acyclique ou cyclique, saturé ou insaturé, facultativement substitué par un ou plusieurs groupe(s) aromatique(s) ou hétérocyclique(s), un groupe acyle aromatique ou un groupe acyle hétérocyclique, dérivés chacun d'un acide carboxylique organique ou d'un acide carbonique organique ou d'un acide sulfonique organique ou d'un acide carbamique organique;

R^2 représente un groupe alkyle en C_1-C_6; un groupe (ar en C_6-C_{10})(alkyle en C_1-C_6);
un groupe (cycloalkyl en C_3-C_7)(alkyle en C_1-C_6); un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)(alkyle en C_1-C_6), dans lequel l'hétérocycle contient 1 à 3 atome(s) d'azote;

R^3 représente un groupe (groupe hétérocyclique condensé au benzène à 9 ou 10 chaînons) (alkyle en C_1-C_6), dans lequel le groupe hétérocyclique contient un à trois atomes d'azote et peut être substitué par un groupe alkyle en C_1-C_6 ou un groupe alcanoyle en C_1-C_6; ou un groupe (ar en C_6-C_{10})(alkyle en C_1-C_6);

R^4 représente un groupe alkyle en C_1-C_6; un groupe (ar en C_6-C_{10})(alkyle en C_1-C_6);
un groupe amino(alkyle en C_1-C_6); un groupe (amino protégé)(alkyle en C_1-C_6); un groupe carboxy(alkyle en C_1-C_6); un groupe (carboxy protégé)(alkyle en C_1-C_6); un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons) (alkyle en C_1-C_6), dans lequel l'hétérocycle contient 1 à 3 atome(s) d'azote; ou un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)-(alkyle en C_1-C_6) dans lequel l'hétérocycle contient 1 ou 2 atomes d'azote et un atome de soufre;

R^5 représente un groupe carboxy;

un groupe carboxy estérifié choisi parmi :
un groupe (alcoxy en C_1-C_6)carbonyle,
un groupe (ar en C_6-C_{10})(alcoxy en C_1-C_6)carbonyle et un groupe (aroyl en C_6-C_{10})(alcoxy en C_1-C_6) carbonyle;
un groupe carboxy amidé choisi parmi :
un groupe carbamoyle,
un groupe N- ou N,N-di(alkyl en C_1-C_6)carbamoyle,
un groupe (alkyl en C_1-C_6)carbamoyle substitué par un ou deux substituants choisis parmi un groupe carboxy et un groupe carboxy protégé,
un groupe N-(alkyl en C_1-C_6)-N-[(carboxy ou carboxy protégé)(alkyl en C_1-C_6)]carbamoyle,
un groupe (ar en C_6-C_{10})(alkyl en C_1-C_6)carbamoyle, un groupe [(ar en C_6-C_{10})(alkyl en C_1-C_6) substitué par un groupe carboxy ou un groupe carboxy protégé]carbamoyle,
un groupe (cycloalkyl en C_3-C_7)carbamoyle,
un groupe N-[(cycloalkyl en C_3-C_7)(alkyl en C_1-C_6) substitué par un groupe carboxy ou un groupe carboxy protégé]carbamoyle,
un groupe (alkyl en C_1-C_6)sulfonylcarbamoyle, un groupe (aryl en C_6-C_{10})sulfonylcarbamoyle,
un groupe [(groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)(alkyl en C_1-C_6) substitué par un groupe carboxy ou un groupe carboxy protégé]carbamoyle, dans lequel l'hétérocycle contient un à trois atome(s) d'azote,
un groupe (alkylène en C_3-C_{10})aminocarbonyle,
un groupe (alkylène en C_3-C_{10})aminocarbonyle substitué par un groupe carboxy ou un groupe carboxy protégé,
un groupe [(alkylène en C_3-C_{10})amino(alkyl en C_1-C_6)]carbamoyle substitué par un à deux substituant (s) choisi(s) parmi un groupe oxo, un groupe carboxy, un groupe carboxy protégé et un groupe carbamoyle, un groupe morpholinocarbonyle,
un groupe (groupe hétéromonocyclique saturé à 5 ou 6 chaînons)carbamoyle, dans lequel l'hétérocycle contient un atome d'azote et un atome d'oxygène,
un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)carbamoyle, dans lequel l'hétérocycle contient un à trois atome(s) d'azote,
un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)carbamoyle, dans lequel l'hétérocycle contient un à deux atome(s) d'azote et un atome de soufre et peut être substitué par un groupe alkyle en C_1-C_6, un groupe (groupe hétérocyclique condensé au benzène à 9 ou 10 chaînons)carbamoyle, dans lequel l'hétérocyclique contient 1 à 2 atome(s) d'azote et un atome de soufre, un groupe (groupe hétéromonocyclique saturé à 5 ou 6 chaînons)(alkyl en C_1-C_6)carbamoyle, dans lequel l'hétérocycle contient un atome d'azote et un atome d'oxygène,
un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)-(alkyle en C_1-C_6)carbonyle, dans lequel l'hétérocycle contient 1 à 3 atome(s) d'azote, un groupe carbazoyle, un groupe di(alkyl en C_1-C_6) carbazoyle;
un groupe carboxy(alkyle en C_1-C_6); ou un groupe (carboxy protégé)(alkyle en C_1-C_6); et

R^6 représente un atome d'hydrogène; ou
un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons) (alkyle en C_1-C_6), dans lequel l'hétérocycle contient un à trois atome(s) d'azote.

6. Composé selon la revendication 5, dans lequel :

R^1 représente un groupe carbamoyle;

un groupe alcanoyle en C_1-C_6;
un groupe amino(alcanoyle en C_1-C_6);
un groupe (alcoxy en C_1-C_6)carbonylamino(alcanoyle en C_1-C_6);
un groupe (cycloalkyl en C_3-C_7)uréido(alcanoyle en C_1-C_6);
un groupe (alcoxy en C_1-C_6)carbonyle;
un groupe (cycloalkyl en C_3-C_7)(alcanoyle en C_1-C_6);
un groupe (cycloalkyl en C_3-C_7)carbonyle;
un groupe (cycloalkyloxy en C_3-C_7)carbonyle;
un groupe benzoyle; un groupe naphtoyle;
un groupe phényl(alcanoyle en C_1-C_6); un groupe naphtyl(alcanoyle en C_1-C_6);

un groupe phényl(alcanoyle en C_1-C_6) substitué par un groupe amino;
un groupe phényl(alcanoyle en C_1-C_6) substitué par un groupe (alcoxy en C_1-C_6)carbonylamino;
un groupe halogénophényl(alcanoyle en C_1-C_6);
un groupe phényl(alcénoyle en C_2-C_6);
un groupe phénylglyoxyloyle;
un groupe phényl(alkyl en C_1-C_6)glyoxyloyle;
un groupe pyridylcarbonyle;
un groupe tétrahydropyridylcarbonyle;
un groupe tétrahydroquinolylcarbonyle;
un groupe tétrahydroisoquinolylcarbonyle;
un groupe morpholinylcarbonyle;
un groupe thiomorpholinylcarbonyle;
un groupe indolylcarbonyle;
un groupe pipérazinylcarbonyle substitué par un à trois substituant(s) choisi(s) parmi un groupe oxo et un groupe alkyle en C_1-C_6;
un groupe pyridyl(alcanoyle en C_1-C_6);
un groupe morpholinylcarbonyl(alcanoyle en C_1-C_6);
un groupe phényl(alkyl en C_1-C_6)sulfonyle;
un groupe N- ou N,N-di(alkyl en C_1-C_{10})carbamoyle; un groupe hydroxy(alkyl en C_1-C_6)carbamoyle;
un groupe carboxy(alkyl en C_1-C_6)carbamoyle;
un groupe (alcoxy en C_1-C_6)carbonyl(alkyl en C_1-C_6)carbamoyle;
un groupe carbamoyl(alkyl en C_1-C_6)carbamoyle;
un groupe [N- ou N,N-di(alkyl en C_1-C_6)carbamoyl](alkyl en C_1-C_6)carbamoyle;
un groupe N-(alkyl en C_1-C_6)-N-[hydroxy(alkyl en C_1-C_6)]carbamoyle;
un groupe N-(alkyl en C_1-C_6)-N-[di(alkyl en C_1-C_6)carbamoyl(alkyl en C_1-C_6)]carbamoyle;
un groupe (alkylène en C_3-C_{10})aminocarbonyle;
un groupe di(alkyl en C_1-C_6)carbamoyl(alkylène en C_3-C_{10})aminocarbonyle;
un groupe N-(alkyl en C_6-C_{10})-N-(cycloalkyl en C_3-C_7)carbamoyle;
un groupe mono- ou di-(cycloalkyl en C_3-C_7)carbamoyle;
un groupe [(cycloalkyl en C_3-C_7) substitué par un groupe hydroxy ou un groupe di(alkyl en C_1-C_6)carbamoyle ou un groupe di(alkyl en C_1-C_6)carbamoyl(alkyl en C_1-C_6)]carbamoyle;
un groupe (cycloalkyl en C_3-C_7)(alkyl en C_1-C_6)carbamoyle;
un groupe [(cycloalkyl en C_3-C_7)(alkyl en C_1-C_6) substitué par un groupe di(alkyl en C_1-C_6)carbamoyle] carbamoyle;
un groupe [phényl(alkyl en C_1-C_6) substitué par un groupe di(alkyl en C_1-C_6)carbamoyle]carbamoyle;
un groupe phénylcarbamoyle, dans lequel le groupe phényle peut être substitué par un à trois substituant (s) choisi(s) parmi un atome d'halogène, un groupe alkyle en C_1-C_6 et un groupe alcoxy en C_1-C_6;
un groupe pyridylcarbamoyle;
un groupe N-(alcoxy en C_1-C_6)carbonylpipéridylcarbamoyle;
un groupe morpholinyl(alkyl en C_1-C_6)carbamoyle; un groupe (alcanoyl en C_1-C_6)carbazoyle;
un groupe (alkylène en C_3-C_{10})aminocarbamoyle;
un groupe N-(cycloalkyl en C_3-C_7)carbamoyl(alkyl en C_1-C_6)carbamoyle;
un groupe (alkylène en C_3-C_{10})aminocarbonyl(alkyl en C_1-C_6)carbamoyle;
un groupe pyridyl(alkyl en C_1-C_6)carbamoyle; ou
un groupe hexahydroazépinylcarbamoyle substitué par un groupe oxo ;

R^2 représente un groupe alkyle en C_1-C_6;
R^3 représente un groupe indolyl(alkyle en C_1-C_6);

un groupe N-(alkyl en C_1-C_6)indolyl(alkyle en C_1-C_6);
un groupe N-(alcanoyl en C_1-C_6)indolyl(alkyle en C_1-C_6);
un groupe phényl(alkyle en C_1-C_6); ou
un groupe naphtyl(alkyle en C_1-C_6);

R^4 représente un groupe alkyle en C_1-C_6;

un groupe amino(alkyle en C_1-C_6);
un groupe mono- ou di- ou tri-phényl(alcoxy en C_1-C_6)carbonylamino(alkyle en C_1-C_6);

un groupe carboxy(alkyle en C_1-C_6);
un groupe mono- ou di- ou tri-phényl(alcoxy en C_1-C_6)carbonyl(alkyle en C_1-C_6);
un groupe phényl(alkyle en C_1-C_6);
un groupe naphtyle(alkyle en C_1-C_6);
un groupe pyridyle(alkyle en C_1-C_6);
un groupe imidazolyl(alkyle en C_1-C_6); ou
un groupe thiazolyl(alkyle en C_1-C_6);

R^5 représente un groupe carboxy;

un groupe (alcoxy en C_1-C_6)carbonyle;
un groupe mono- ou di- ou tri-phényl(alcoxy en C_1-C_6)carbonyle;
un groupe benzoyl(alcoxy en C_1-C_6)carbonyle;
un groupe carbamoyle;
un groupe N- ou N,N-di(alkyl en C_1-C_6)carbamoyle;
un groupe (alkyl en C_1-C_6)carbamoyle substitué par un ou deux substituants choisis parmi un groupe carboxy,
un groupe (alcoxy en C_1-C_6)carbonyle, un groupe mono- ou di- ou tri-phényl(alcoxy en C_1-C_6)carbonyle et un groupe benzoyl(alcoxy en C_1-C_6)-carbonyle;
un groupe N-(alkyl en C_1-C_6)-N-[carboxy(ou(alcoxy en C_1-C_6)carbonyl(alkyl en C_1-C_6)]carbamoyle;
un groupe phényl(alkyl en C_1-C_6)carbamoyle;
un groupe [phényl(alkyl en C_1-C_6) substitué par un groupe carboxy ou un groupe (alcoxy en C_1-C_6) carbonyle]carbamoyle;
un groupe (cycloalkyl en C_3-C_7)carbamoyle;
un groupe [carboxy(cycloalkyl en C_3-C_7)(alkyl en C_1-C_6)]carbamoyle;
un groupe [(alcoxy en C_1-C_6)carbonyl(cycloalkyl en C_3-C_7)(alkyl en C_1-C_6)]carbamoyle;
un groupe (alkyl en C_1-C_6)sulfonylcarbamoyle;
un groupe phénylsulfonylcarbamoyle,
un groupe [pyridyl(alkyl en C_1-C_6) substitué par un groupe carboxy ou un groupe (alcoxy en C_1-C_6)carbonyl]carbamoyle;
un groupe (alkylène en C_3-C_{10})aminocarbonyle;
un groupe (alkylène en C_3-C_{10})aminocarbonyle substitué par un groupe carboxy ou un groupe (alcoxy en C_1-C_6)carbonyle;
un groupe [(alkylène en C_3-C_{10})amino(alkyle en C_1-C_6)]carbamoyle substitué par un à deux substituant (s) choisi(s) parmi un groupe oxo, un groupe carboxy, un groupe (alcoxy en C_1-C_6)carbonyle et un groupe carbamoyle;
un groupe morpholinocarbonyle;
un groupe morpholinylcarbamoyle;
un groupe pyridylcarbamoyle;
un groupe thiazolylcarbamoyle;
un groupe (alkyle en C_1-C_6)thiadiazolylcarbamoyle;
un groupe benzothiazolylcarbamoyle;
un groupe morpholinyl(alkyl en C_1-C_6)carbamoyle;
un groupe pyridyl(alkyl en C_1-C_6)carbamoyle;
un groupe carbazoyle,
un groupe di(alkyl en C_1-C_6)carbazoyle;
un groupe carboxy(alkyle en C_1-C_6);
un groupe (alcoxy en C_1-C_6)carbonyl(alkyle en C_1-C_6); ou
un groupe benzoyl(alcoxy en C_1-C_6)carbonyl(alkyle en C_1-C_6), et

R^6 et R^7 représentent chacun un atome d'hydogène.

7. Composé selon la revendication 6, dans lequel :

R^1 représente un groupe N- ou N,N-di(alkyl en C_1-C_{10})carbamoyle,
un groupe N-(alkyl en C_1-C_6)-N-(cycloalkyl en C_3-C_7)carbamoyle, un groupe N- ou N,N-di(cycloalkyl en C_3-C_7)carbamoyle, un groupe N-(alkyl en C_1-C_6)-N-[N,N-di(alkyl en C_1-C_6)carbamoyl(alkyl en C_1-C_6)]carbamoyle, un groupe phénylcarbamoyle, un groupe (alkylène en C_3-C_{10})aminocarbonyle ou un groupe N-(alkyl en

C_1-C_6)-N-[hydroxy(alkyl en C_1-C_6)]carbamoyle,

R^2 représente un groupe alkyle en C_1-C_6,

R^3 représente un groupe indolyl(alkyle en C_1-C_6), un groupe N-(alcanoyl en C_1-C_6)indolyl(alkyle en C_1-C_6) ou un groupe N-(alkyl en C_1-C_6)indolyl(alkyle en C_1-C_6),

R^4 représente un groupe pyridyl(alkyle en C_1-C_6) ou phényl(alkyle en C_1-C_6),

R^5 représente un groupe carboxy,

un groupe (alcoxy en C_1-C_6)carbonyle,
un groupe carbamoyle ou
un groupe N- ou N,N-di(alkyl en C_1-C_6)carbamoyle, et

A représente un groupe méthylène ou un groupe -NH-.

8. Composé selon la revendication 7, dans lequel :

R^1 représente un groupe isopropylcarbamoyle, un groupe 2-méthylbutylcarbamoyle, un groupe heptylcarbamoyle, un groupe diméthylcarbamoyle, un groupe diéthylcarbamoyle, un groupe dipropylcarbamoyle, un groupe diisopropylcarbamoyle, un groupe dibutylcarbamoyle, un groupe diisobutylcarbamoyle, un groupe pyrrolidin-1-ylcarbonyle, un groupe pipéridin-1-ylcarbonyle, un groupe 3,5- ou 2,6-diméthylpipéridin-1-ylcarbonyle, un groupe hexahydro-1H-azépin-1-ylcarbonyle ou un groupe octahydroazocin-1-ylcarbonyle,

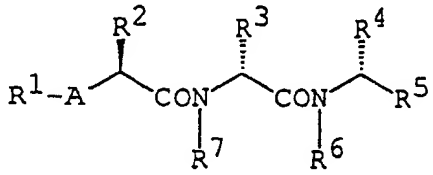
R^2 représente un groupe isobutyle,

R^3 représente un groupe indol-3-ylméthyle, un groupe N-formylindol-3-ylméthyle, un groupe N-méthylindol-3-ylméthyle, un groupe N-éthylindol-3-ylméthyle, un groupe N-propylindol-3-ylméthyl ou un groupe N-isobutylindol-3-yl-méthyle,

R^4 représente un groupe 2-pyridylméthyle ou benzyle,

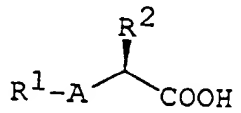
R^5 représente un groupe carboxy, un groupe méthoxycarbonyle, un groupe éthoxycarbonyle, un groupe carbamoyle, un groupe méthylcarbamoyle, un groupe éthylcarbamoyle, un groupe propylcarbamoyle, un groupe isopropylcarbamoyle, un groupe butylcarbamoyle, un groupe N,N-diméthylcarbamoyle ou un groupe N,N-diéthylcarbamoyle.

9. Procédé pour la préparation d'un composé de type peptide de formule (I) :



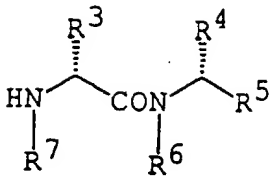
dans laquelle R^1, R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis dans la revendication 1, ou des sels de celui-ci, qui comprend les étapes consistant à :

(a) faire réagir un composé de formule :



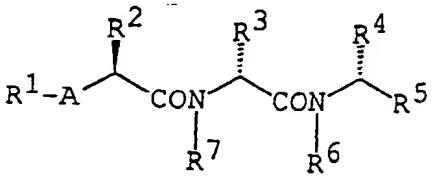
(II)

dans laquelle R^1, R^2 et A sont chacun tels que définis ci-dessus, ou son dérivé réactif au niveau du groupe carboxy ou un sel de celui-ci, avec un composé de formule :



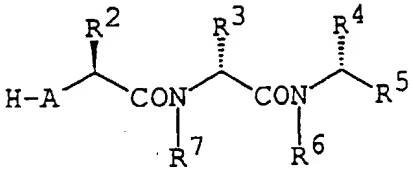
(III)

dans laquelle R^3, R^4, R^5, R^6, et R^7 sont chacuns tels que définis ci-dessus, ou son dérivé réactif au niveau du groupe amino, ou un sel de celui-ci, pour obtenir un composé de formule :



(I)

dans laquelle R^1, R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus,
ou un sel de celui-ci; ou
(b) faire réagir un composé de formule :

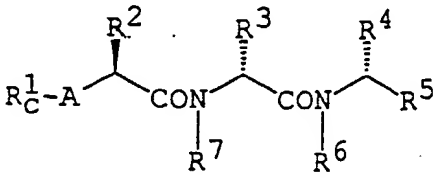


(I-a)

dans laquelle R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacuns tels que définis ci-dessus,
ou son dérivé réactif au niveau du groupe amino, ou un sel de celui-ci, avec un composé de formule :

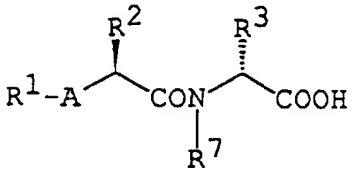
$$R_c^1\text{-OH} \qquad \text{(IV)}$$

dans laquelle R_c^1 représente un groupe acyle, ou son dérivé réactif au niveau du groupe carboxy, ou un sel de celui-ci, pour obtenir un composé de formule :



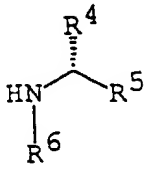
(I-b)

dans laquelle R^1, R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus,
ou un sel de celui-ci; ou
(c) faire réagir un composé de formule :



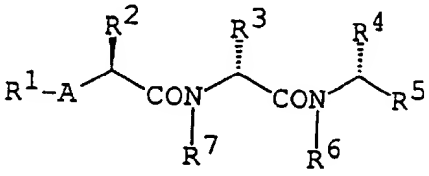
(V)

dans laquelle R^1, R^2, R^3, R^7 et A sont chacun tels que définis ci-dessus, ou son dérivé réactif au niveau du groupe carboxy, ou un sel de celui-ci, avec un composé de formule :



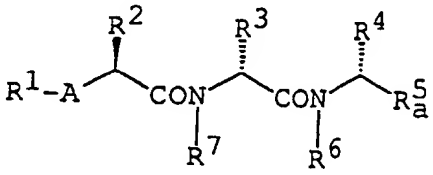
(VI)

dans laquelle R^4, R^5 et R^6 sont chacun tels que définis ci-dessus,
ou son dérivé réactif au niveau du groupe amino, ou un sel de celui-ci pour obtenir un composé de formule :



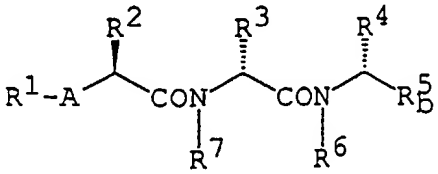
(I)

dans laquelle R^1, R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus,
ou un sel de celui-ci; ou
(d) soumettre un composé de formule :



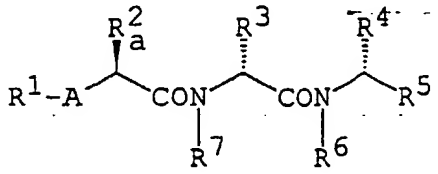
(I-c)

dans laquelle R^1, R^2, R^3, R^4, R^6, R^7 et A sont chacun tels que définis ci-dessus, et
R^5_a représente un groupe carboxy protégé ou un groupe carboxy(alkyle en C_1-C_6),
ou un sel de celui-ci, à une réaction d'élimination du groupe protecteur du groupe carboxy pour obtenir un composé de formule :



(I-d)

dans laquelle R^1, R^2, R^3, R^4, R^6, R^7 et A sont chacun tels que définis ci-dessus, et
R^5_b représente un groupe carboxy ou un groupe carboxy(alkyle en C_1-C_6),
ou un sel de celui-ci; ou
(e) soumettre un composé de formule :



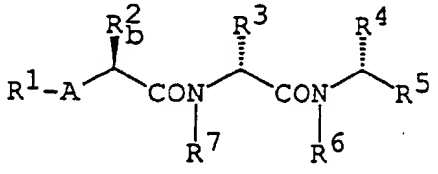
(I-e)

dans laquelle R^1, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et

R^2_a représente un groupe (groupe hétérocyclique)(alkyle en C_1-C_6) contenant un groupe imino protégé, facultativement substitué par un ou plusieurs substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6; un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro et un groupe cyano;
ledit groupe hétérocyclique étant :

un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 5 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote, ou
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,

ou un sel de celui-ci, à une réaction d'élimination du groupe protecteur du groupe imino dans R^2_a pour obtenir un composé de formule :



(I-f)

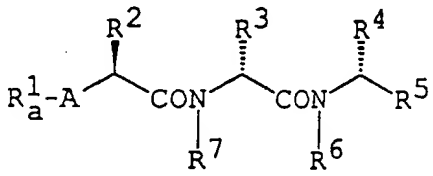
dans laquelle R^1, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et

R^2_b représente un groupe (groupe hétérocyclique) (alkyle en C_1-C_6) contenant un groupe imino, facultativement substitué par un ou plusieurs substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6; un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro et un groupe cyano;
ledit groupe hétérocyclique étant :

un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 5 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1

à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,

ou un sel de celui-ci; ou
(f) soumettre un composé de formule :

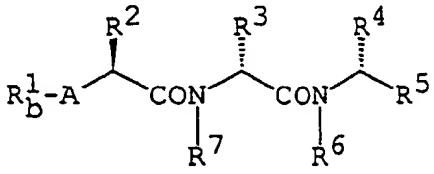


(I-g)

dans laquelle R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et

R^1_a représente un groupe acyle substitué par un groupe amino protégé,

ou un sel de celui-ci, à une réaction d'élimination du groupe protecteur du groupe amino pour obtenir un composé de formule :

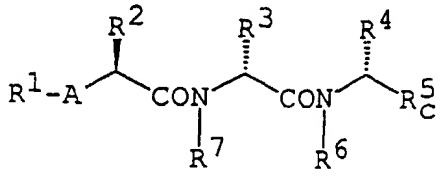


(I-h)

dans laquelle R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et

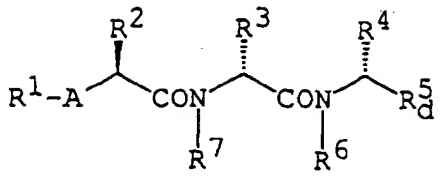
R^1_b représente un groupe acyle substitué par un groupe amino, ou un sel de celui-ci; ou

(g) faire réagir un composé de formule :



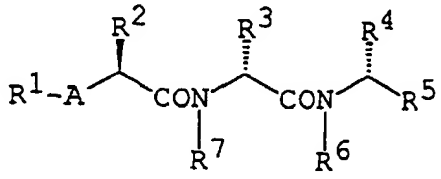
(I-i)

dans laquelle R^1, R^2, R^3, R^4, R^6, R^7 et A sont chacun tels que définis ci-dessus, et
R^5_c représente un groupe carboxy estérifié tel que défini dans la revendication 4, ou son dérivé réactif au niveau du groupe carboxy, ou un sel de celui-ci, avec une amine facultativement substituée, ou un sel de celle-ci pour obtenir un composé de formule :



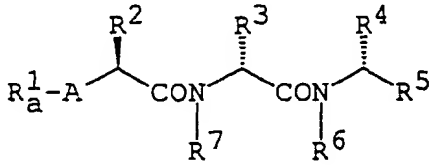
(I-j)

dans laquelle R^1, R^2, R^3, R^4, R^6, R^7 et A sont chacun tels que définis ci-dessus, et
R^5_d représente un groupe carboxy amidé tel que défini dans la revendication 4, ou un sel de celui-ci; ou
(h) acyler le groupe amino dans R^1_b d'un composé de formule :



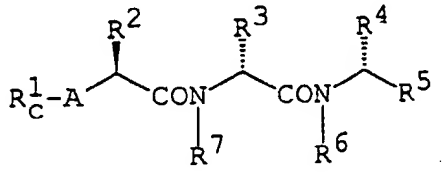
(I-h)

dans laquelle R^1_a, R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus,
ou un sel de celui-ci, pour obtenir un composé de formule :



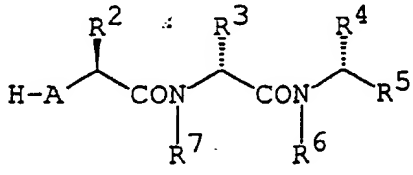
(I-g)

dans laquelle R^1_a, R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus,
ou un sel de celui-ci; ou
(i) soumettre un composé de formule :



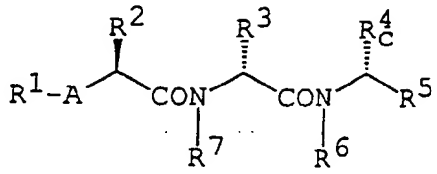
(I-b)

dans laquelle R^1_c, R^2, R^3, R^4, R^6, R^7 et A sont chacun tels que définis ci-dessus,
ou un sel de celui-ci, à une réaction d'élimination du groupe acyle de R^1_c pour obtenir un composé de formule :



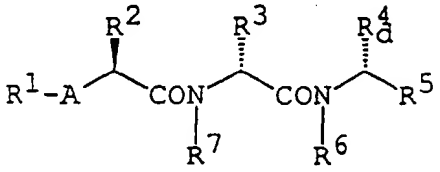
(I-a)

dans laquelle R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus,
ou un sel de celui-ci; ou
(j) soumettre un composé de formule :



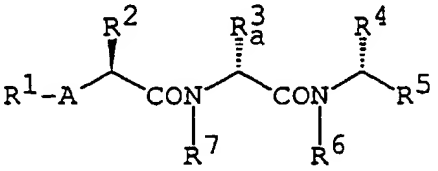
(I-k)

dans laquelle R^1, R^2, R^3, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et
R^4_c représente un groupe (carboxy protégé)(alkyle en C_1-C_6), ou un sel de celui-ci, à une réaction d'élimination du groupe protecteur du groupe carboxy dans R^4_c pour obtenir un composé de formule :



(I-l)

dans laquelle R^1, R^2, R^3, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et
R^4_d représente un groupe carboxy(alkyle en C_1-C_6),
ou un sel de celui-ci; ou
(k) soumettre un composé de formule :



(I-m)

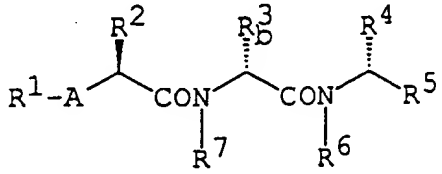
dans laquelle R^1, R^2, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et

R^3_a représente un (groupe hétérocyclique)(alkyle en C_1-C_6) contenant un groupe imino protégé, facultativement substitué par un ou plusieurs substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6; un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro et un groupe cyano;
ledit groupe hétérocyclique étant :

un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 5 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,

un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote, ou
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,

ou un sel de celui-ci à une réaction d'élimination du groupe protecteur du groupe imino dans R_a^3 pour obtenir un composé de formule :



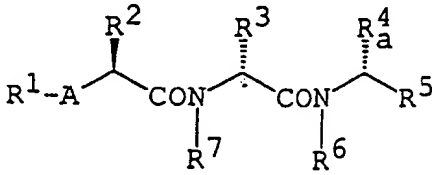
(I-n)

dans laquelle R^1, R^2, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et

R_b^3 représente un groupe (groupe hétérocyclique) (alkyle en C_1-C_6) contenant un groupe imino, facultativement substitué par un ou plusieurs substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6; un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro et un groupe cyano,
ledit groupe hétérocyclique étant :

un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 5 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote, ou
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,

ou un sel de celui-ci; ou
(l) soumettre un composé de formule :



(I-o)

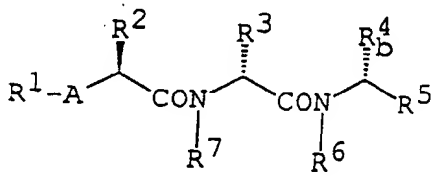
dans laquelle R^1, R^2, R^3, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et

R_a^4 représente un groupe (amino protégé) (alkyle en C_1-C_6) ou un groupe (groupe hétérocyclique) (alkyle en C_1-C_6) contenant un groupe imino protégé, ledit groupe hétérocyclique étant :

un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,

un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 8 à 12 chaînons contenant 1 à 5 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome (s) d'azote, ou
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
sachant que ledit groupe hétérocyclique peut être substitué par un ou deux substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6, un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro et un groupe cyano,

ou un sel de celui-ci, à une réaction d'élimination du groupe protecteur du groupe amino ou du groupe imino dans R^4_a pour obtenir un composé de formule :



(I-p)

dans laquelle R^1, R^2, R^3, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et
R^4_b représente un groupe amino(alkyle en C_1-C_6) ou un un groupe (groupe hétérocyclique) (alkyle en C_1-C_6) contenant un groupe imino, ledit groupe hétérocyclique étant :

un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 5 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome (s) d'azote, ou
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,

sachant que ledit groupe hétérocyclique peut être substitué par un ou deux substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6, un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro et un groupe cyano,

ou un sel de celui-ci.

10. Composition pharmaceutique qui comprend un composé selon la revendication 1 ou un sel pharmaceutiquement acceptable de celui-ci et un véhicule ou un excipient pharmaceutiquement acceptable.

11. Procédé pour préparer une composition pharmaceutique qui comprend l'étape consistant à mélanger un composé selon la revendication 1 ou des sels pharmaceutiquement acceptables de celui-ci avec un véhicule ou un excipient pharmaceutiquement acceptable.

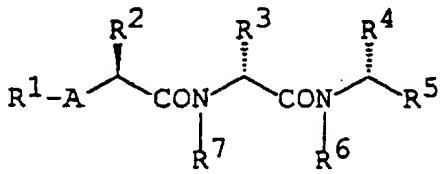
12. Composé selon la revendication 1 ou sels pharmaceutiquement acceptables de celui-ci destinés à être utilisés comme médicament.

13. Composé selon la revendication 1 ou sels pharmaceutiquement acceptables de celui-ci destinés à être utilisés comme agent antagoniste de l'endothéline.

14. Utilisation d'un composé selon la revendication 1 ou de sels pharmaceutiquement acceptables de celui-ci pour fabriquer un médicament pour le traitement des maladies à médiation d'endothéline.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation d'un composé de type peptide de formule (I) :



(I)

ayant une activité antagoniste des récepteurs de l'endothéline,
formule dans laquelle :

R^1 représente un atome d'hydrogène ou un groupe acyle,
R^2 représente un groupe alkyle en C_1-C_6;

un groupe (ar en C_6-C_{10})(alkyle en C_1-C_6) facultativement substitué par un ou plusieurs substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6; un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro et un groupe cyano; un groupe cyclo(alkyl en C_1-C_6) (alkyle en C_1-C_6); ou un groupe (groupe hétérocyclique)(alkyle en C_1-C_6) facultativement substitué par un ou plusieurs substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6; un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro, un groupe cyano et un groupe protecteur du groupe imino; ledit groupe hétérocyclique étant
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 5 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome (s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant un atome de soufre, ou
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,

R^3 représente un groupe (groupe hétérocyclique) (alkyle en C_1-C_6) ou

un groupe (ar en C_6-C_{10})(alkyle en C_1-C_6), chacun facultativement substitué par un ou plusieurs substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6; un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro, un groupe cyano et un groupe protecteur du groupe imino, ledit groupe hétérocyclique étant
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 8 à 12 chaînons contenant 1 à 5 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome (s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant un atome de soufre, ou
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,

R^4 représente un groupe alkyle en C_1-C_6), un groupe (ar en C_6-C_{10})(alkyle en C_1-C_6), un groupe amino(alkyle en C_1-C_6), un groupe (amino protégé) (alkyle en C_1-C_6), un groupe carboxy(alkyle en C_1-C_6), un groupe carboxy protégé) (alkyle en C_1-C_6) ou un groupe (groupe hétéro-cyclique) (alkyle en C_1-C_6) facultativement substitué,
ledit groupe hétérocyclique étant

un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 8 à 12 chaînons contenant 1 à 5 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
- un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome (s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant un atome de soufre, ou
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,

sachant que ledit groupe hétérocyclique peut être substitué par un ou deux substituants(s) approprié(s) choisi (s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6, un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro, un groupe cyano et un groupe protecteur du groupe imino,

R^5 représente un groupe carboxy, un groupe carboxy protégé, un groupe carboxy(alkyle en C_1-C_6), ou un groupe (carboxy protégé)(alkyle en C_1-C_6),

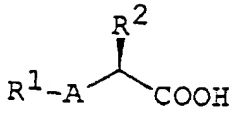
R^6 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_6 facultativement substitué,

R^7 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_6, et

A représente -O-, -NH-, un groupe (alkyl en C_1-C_6)-imino ou un groupe alkylène en C_1-C_6, sous réserve que lorsque R^3 représente un groupe indol-3-ylméthyle ou un groupe (N-formylindol-3-yl)méthyle, alors R^2 ne représente pas un groupe alkyle en C_3-C_5,

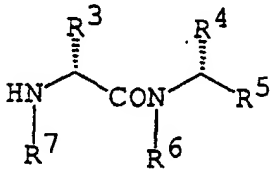
ou un sel pharmaceutiquement acceptable de ce composé, qui comprend les étapes consistant à

(a) faire réagir un composé de formule :



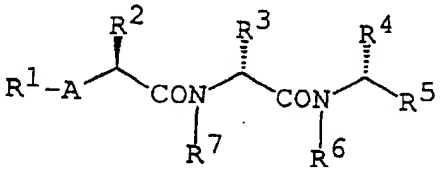
(II)

dans laquelle R^1, R^2 et A sont chacun tels que définis ci-dessus, ou son dérivé réactif au niveau du groupe carboxy ou un sel de celui-ci, avec un composé de formule :



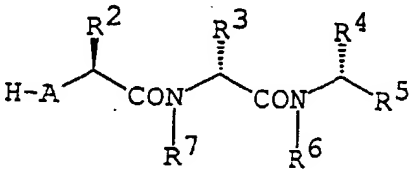
(III)

dans laquelle R^3, R^4, R^5, R^6, et R^7 sont chacuns tels que définis ci-dessus, ou son dérivé réactif au niveau du groupe amino, ou un sel de celui-ci, pour obtenir un composé de formule :



(I)

dans laquelle R^1, R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus,
ou un sel de celui-ci; ou
(b) faire réagir un composé de-formule :

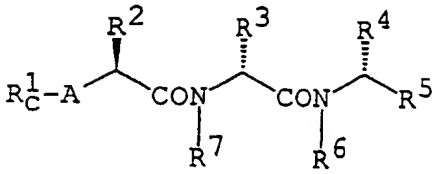


(I-a)

dans laquelle R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacuns tels que définis ci-dessus,
ou son dérivé réactif au niveau du groupe amino, ou un sel de celui-ci, avec un composé de formule :

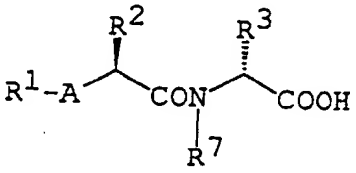
$$R_c^1\text{-OH} \qquad \text{(IV)}$$

dans laquelle R_c^1 représente un groupe acyle,
ou son dérivé réactif au niveau du groupe carboxy, ou un sel de celui-ci, pour obtenir un composé de formule :



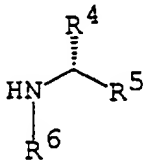
(I-b)

dans laquelle R^1, R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus,
ou un sel de celui-ci; ou
(c) faire réagir un composé de formule :



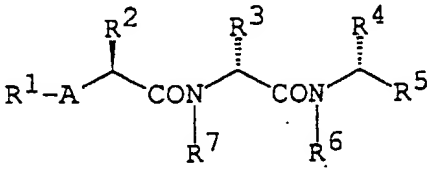
(V)

dans laquelle R^1, R^2, R^3, R^7 et A sont chacun tels que définis ci-dessus, ou son dérivé réactif au niveau du groupe carboxy, ou un sel de celui-ci, avec un composé de formule :



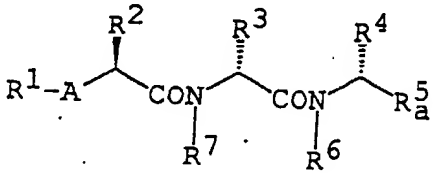
(VI)

dans laquelle R^4, R^5 et R^6 sont chacun tels que définis ci-dessus,
ou son dérivé réactif au niveau du groupe amino, ou un sel de celui-ci pour obtenir un composé de formule :



(I)

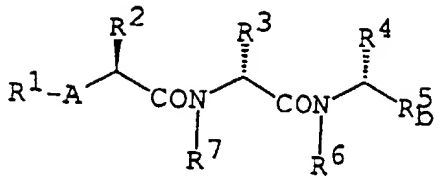
dans laquelle R^1, R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus,
ou un sel de celui-ci; ou
(d) soumettre un composé de formule :



(I-c)

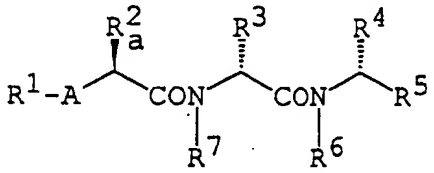
dans laquelle R^1, R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et
R^5_a représente un groupe carboxy protégé ou un groupe carboxy(alkyle en C_1-C_6),
ou un sel de celui-ci, à une réaction d'élimination du groupe protecteur du groupe carboxy pour obtenir un

composé de formule :



(I-d)

dans laquelle R^1, R^2, R^3, R^4, R^6, R^7 et A sont chacun tels que définis ci-dessus, et
R^5_b représente un groupe carboxy ou un groupe carboxy(alkyle en C_1-C_6),
ou un sel de celui-ci; ou
(e) soumettre un composé de formule :



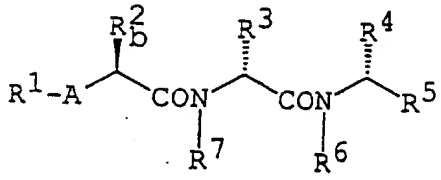
(I-e)

dans laquelle R^1, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et

R^2_a représente un groupe (groupe hétérocyclique) (alkyle en C_1-C_6) contenant un groupe imino protégé, facultativement substitué par un ou plusieurs substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6; un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro et un groupe cyano;
ledit groupe hétérocyclique étant :

un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 5 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote, ou
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,

ou un sel de celui-ci à une réaction d'élimination du groupe protecteur du groupe imino dans R^2_a pour obtenir un composé de formule :



(I-f)

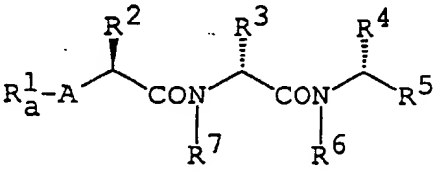
dans laquelle R^1, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et

R^2_b représente un groupe (groupe hétérocyclique) (alkyle en C_1-C_6) contenant un groupe imino facultativement substitué par un ou plusieurs substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6; un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro et un groupe cyano;
ledit groupe hétérocyclique étant :

un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 5 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,

ou un sel de celui-ci;

(f) soumettre un composé de formule :

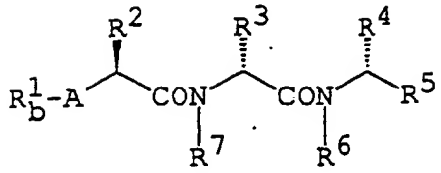


(I-g)

dans laquelle R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et

R^1_a représente un groupe acyle substitué par un groupe amino protégé,

ou un sel de celui-ci, à une réaction d'élimination du groupe protecteur du groupe amino pour obtenir un composé de formule :

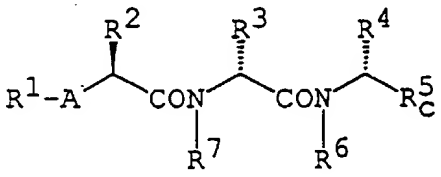


(I-h)

dans laquelle R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et

R^1_b représente un groupe acyle substitué par un groupe amino, ou un sel de celui-ci; ou

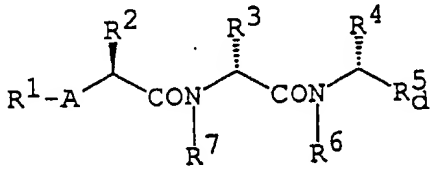
(g) faire réagir un composé de formule :



(I-i)

dans laquelle R^1, R^2, R^3, R^4, R^5, R^7 et A sont chacun tels que définis ci-dessus, et

R^5_c représente un groupe carboxy estérifié tel que défini dans la revendication 4, ou son dérivé réactif au niveau du groupe carboxy, ou un sel de celui-ci, avec une amine facultativement substituée, ou un sel de celle-ci pour obtenir un composé de formule :

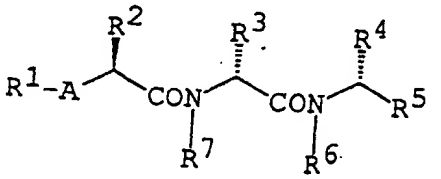


(I-j)

dans laquelle R^1, R^2, R^3, R^4, R^6, R^7 et A sont chacun tels que définis ci-dessus, et

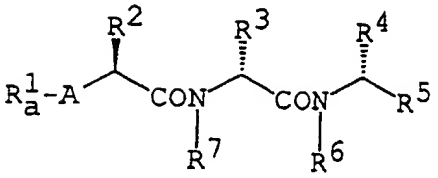
R^5_d représente un groupe carboxy amidé tel que défini dans la revendication 4, ou un sel de celui-ci; ou

(h) acyler le groupe amino dans R^1_b d'un composé de formule :



(I-h)

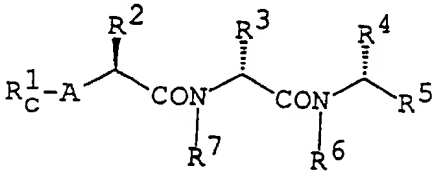
dans laquelle R^1_b, R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, ou un sel de celui-ci, pour obtenir un composé de formule :



(I-g)

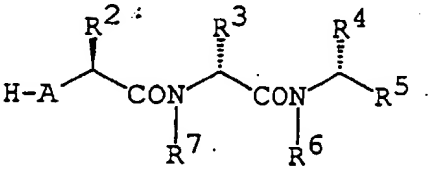
dans laquelle R^1_a, R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, ou un sel de celui-ci; ou

(i) soumettre un composé de formule :



(I-b)

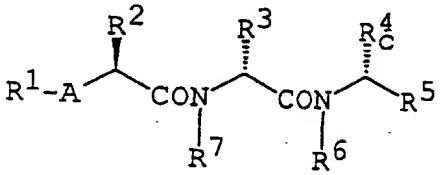
dans laquelle R^1_c, R^2, R^3, R^4, R^6, R^7 et A sont chacun tels que définis ci-dessus, ou un sel de celui-ci, à une réaction d'élimination du groupe acyle de R^1_c pour obtenir un composé de formule :



(I-a)

dans laquelle R^2, R^3, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, ou un sel de celui-ci; ou

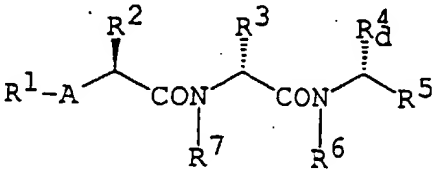
(j) soumettre un composé de formule :



(I-k)

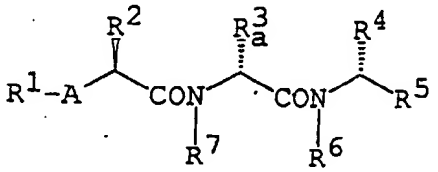
dans laquelle R^1, R^2, R^3, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et

R^4_c représente un groupe carboxy protégé (alkyle en C_1-C_6), ou un sel de celui-ci, à une réaction d'élimination du groupe protecteur du groupe carboxy dans R^4_c pour obtenir un composé de formule :



(I-l)

dans laquelle R^1, R^2, R^3, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et
R^4_d représente un groupe carboxy(alkyle en CiC_6),
ou un sel de celui-ci; ou
(k) soumettre un composé de formule :



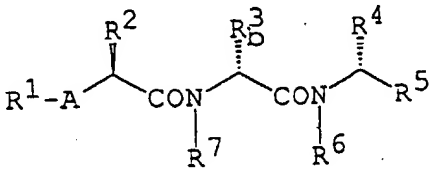
(I-m)

dans laquelle R^1, R^2, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et

R^3_a représente un groupe (groupe hétérocyclique) (alkyle en C_1-C_6) contenant un groupe imino protégé, facultativement substitué par un ou plusieurs substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6; un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro et un groupe cyano;
ledit groupe hétérocyclique étant :

un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 5 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote, ou
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,

ou un sel de celui-ci, à une réaction d'élimination du groupe protecteur du groupe imino dans R^a_a pour obtenir un composé de formule :



(I-n)

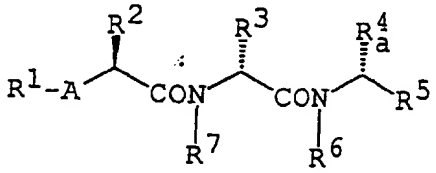
dans laquelle R^1, R^2, R^4, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et

R^3_b représente un groupe (groupe hétérocyclique) (alkyle en C_1-C_6) contenant un groupe imino facultativement substitué par un ou plusieurs substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6; un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro et un groupe cyano,
ledit groupe hétérocyclique étant :

un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,

un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 5 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote, ou
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,

ou un sel de celui-ci; ou
(l) soumettre un composé de formule :

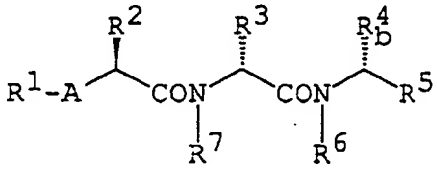


(I-o)

dans laquelle R^1, R^2, R^3, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et
R^4_a représente un groupe (amino protégé) (alkyle en C_1-C_6) ou un groupe (groupe hététrocyclique)(alkyle en C_1-C_6) contenant un groupe imino protégé, ledit groupe hétérocyclique étant :

un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 8 à 12 chaînons contenant 1 à 5 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome (s) d'azote, ou
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,

sachant que ledit groupe hétérocyclique peut être substitué par un ou deux substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6, un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro et un groupe cyano,
ou un sel de celui-ci, à une réaction d'élimination du groupe protecteur du groupe amino ou du groupe imino dans R^4_a pour obtenir un composé de formule :



(I-p)

dans laquelle R^1, R^2, R^3, R^5, R^6, R^7 et A sont chacun tels que définis ci-dessus, et

R^4_b représente un groupe amino(alkyle en C_1-C_6) ou un groupe (groupe hétérocyclique) (alkyle en C_1-C_6) contenant un groupe imino,

ledit groupe hétérocyclique étant :

un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 4 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 5 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) d'oxygène et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,
un groupe hétéromonocyclique saturé à 3 à 8 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome (s) d'azote, ou
un groupe hétérocyclique insaturé condensé à 7 à 12 chaînons contenant 1 à 2 atome(s) de soufre et 1 à 3 atome(s) d'azote,

sachant que ledit groupe hétérocyclique peut être substitué par un ou deux substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6, un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro et un groupe cyano,

ou un sel de celui-ci.

2. Procédé selon la revendication 1, dans lequel :

R^3 représente un groupe (groupe hétérocyclique) (alkyle en C_1-C_6) ou un groupe (ar en C_6-C_{10})(alkyle en C_1-C_6), chacun facultativement substitué par un ou plusieurs substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6; un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro, un groupe cyano et un groupe protecteur du groupe imino, ledit groupe hétérocyclique étant
un groupe hétérocyclique insaturé condensé à 8 à 12 chaînons contenant 1 à 5 atome(s) d'azote.

3. Procédé selon la revendication 2, dans lequel :

R^3 représente un groupe (groupe hétérocyclique condensé au benzène à 9 ou 10 chaînons) (alkyle en C_1-C_6), dans lequel le groupe hétérocyclique contient un à trois atome(s) d'azote et peut être substitué par un ou plusieurs substituant(s) approprié(s) choisi(s) parmi un groupe hydroxy, un groupe hydroxy protégé, un atome d'halogène, un groupe alcoxy en C_1-C_6, un groupe alkyle en C_1-C_6, un groupe amino, un groupe nitro, un groupe cyano et un groupe protecteur du groupe imino;
ou un groupe (ar en C_6-C_{10})(alkyle en C_1-C_6).

4. Procédé selon la revendication 3, dans lequel

R^5 représente un groupe carboxy, un groupe carboxy estérifié choisi parmi :

un groupe (alcoxy en C_1-C_6)carbonyle,
un groupe (ar en C_6-C_{10})(alcoxy en C_1-C_6)carbonyle, et
un groupe (aroyl en C_6-C_{10})(alcoxy en C_1-C_6)carbonyle;
un groupe carboxy amidé, choisi parmi :
un groupe carbamoyle,
un groupe N- ou N,N-di(alkyl en C_1-C_6)carbamoyle,
un groupe (alkyl en C_1-C_6) carbamoyle substitué par un ou deux substituant(s) choisi(s) parmi un groupe carboxy et un groupe carboxy protégé,
un groupe N-(alkyl en C_1-C_6)-N-[carboxy- ou (carboxy protégé) (alkyl en C_1-C_6)]carbamoyle,

un groupe (ar en C_6-C_{10})(alkyl en C_1-C_6)carbamoyle,
un groupe (ar en C_6-C_{10})(alkyl en C_1-C_6)carbamoyle substitué par un groupe carboxy ou carboxy protégé,
un groupe (cycloalkyl en C_3-C_7)carbamoyle,
Un groupe N-[(cycloalkyl en C_3-C_7)(alkyl en C_1-C_6) substitué par un groupe carboxy ou carboxy protégé] carbamoyle,
un groupe (alkyl en C_1-C_6)sulfonylcarbamoyle, un groupe (aryl en C_6-C_{10})sulfonylcarbamoyle,
un groupe [(groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)(groupe alkyl en C_1-C_6) substitué par un groupe carboxy ou un groupe carboxy protégé]carbamoyle dans lequel l'hétérocyclique contient un à trois atome(s) d'azote,
un groupe (alkylène en C_3-C_{10})aminocarbonyle,
un groupe (alkylène en C_3-C_{10})aminocarbonyle substitué par un groupe carboxy ou un groupe carboxy protégé,
un groupe [(alkylène en C_3-C_{10})amino(alkyl en C_1-C_6)]carbamoyle substitué par un ou deux substituant (s) choisi(s) parmi un groupe oxo, un groupe carboxy, un groupe carboxy protégé et un groupe carbamoyle,
un groupe morpholinocarbonyle,
un groupe (groupe hétéromonocyclique saturé à 5 ou 6 chaînons) carbamoyle, dans lequel l'hétérocyclique contient un atome d'azote et un atome d'oxygène,
un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)carbamoyle, dans lequel l'hétérocyclique contient 1 à 3 atomes d'azote,
un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)carbamoyle, dans lequel l'hétérocycle contient 1 à 2 atome(s) d'azote et un atome de soufre et peut être substitué par un groupe alkyle en C_1-C_6, un groupe (groupe hétérocyclique condensé au benzène à 9 ou 10 chaînons)carbamoyle, dans lequel l'hétérocyclique contient un à deux atome(s) d'azote et un atome de soufre, un groupe (groupe hétéromonocyclique saturé à 5 ou 6 chaînons)(alkyl en C_1-C_6)carbamoyle, dans lequel l'hétérocyclique contient un atome d'azote et un atome d'oxygène, un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)(alkyl en C_1-C_6)carbonyle, dans lequel l'hétérocycle contient 1 à 3 atome(s) d'azote, un groupe carbazoyle, un groupe di(alkyl en C_1-C_6)carbazoyle;
un groupe carboxy(alkyle en C_1-C_6); ou
un groupe (carboxy protégé)(alkyle en C_1-C_6); et

R^6 représente un atome d'hydrogène ou un groupe (groupe hétérocyclique)(alkyle en C_1-C_6), dans lequel ledit groupe hétérocyclique est un groupe hétéromonocyclique insaturé à 3 à 8 chaînons contenant 1 à 4 atome (s) d'azote.

5. Procédé selon la revendication 4, dans laquelle :

R^1 représente un groupe carbamoyle; un groupe acyle aliphatique, acyclique ou cyclique, saturé ou insaturé, facultativement substitué par un ou plusieurs groupe(s) aromatique(s) ou hétérocyclique(s), un groupe acyle aromatique ou un groupe acyle hétérocyclique, dérivés chacun d'un acide carboxylique organique ou d'un acide carbonique organique ou d'un acide sulfonique organique ou d'un acide carbamique organique;
R^2 représente un groupe alkyle en C_1-C_6; un groupe (ar en C_6-C_{10})(alkyle en C_1-C_6);
un groupe (cycloalkyl en C_3-C_7)(alkyle en C_1-C_6); un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)(alkyle en C_1-C_6), dans lequel l'hétérocycle contient 1 à 3 atome(s) d'azote;
R^3 représente un groupe (groupe hétérocyclique condensé au benzène à 9 ou 10 chaînons) (alkyle en C_1-C_6), dans lequel le groupe hétérocyclique contient un à trois atomes d'azote et peut être substitué par un groupe alkyle en C_1-C_6 ou un groupe alcanoyle en C_1-C_6; ou un groupe (ar en C_6-C_{10})(alkyle en C_1-C_6);
R^4 représente un groupe alkyle en C_1-C_6; un groupe (ar en C_6-C_{10})(alkyle en C_1-C_6);
un groupe amino(alkyle en C_1-C_6); un groupe (amino protégé)(alkyle en C_1-C_6); un groupe carboxy(alkyle en C_1-C_6); un groupe (carboxy protégé) (alkyle en C_1-C_6); un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)(alkyle en C_1-C_6), dans lequel l'hétérocycle contient 1 à 3 atomes d'azote; ou un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)-(alkyle en C_1-C_6) dans lequel l'hétérocycle contient 1 ou 2 atomes d'azote et un atome de soufre;
R^5 représente un groupe carboxy;

un groupe carboxy estérifié choisi parmi :
un groupe (alcoxy en C_1-C_6)carbonyle,
un groupe (ar en C_6-C_{10})(alcoxy en C_1-C_6)carbonyle et

un groupe (aroyl en C_6-C_{10})(alcoxy en C_1-C_6)carbonyle;
un groupe carboxy amidé choisi parmi :
un groupe carbamoyle,
un groupe N- ou N,N-di(alkyl en C_1-C_6)carbamoyle,
un groupe (alkyl en C_1-C_6)carbamoyle substitué par un ou deux substituants choisis parmi un groupe carboxy et un groupe carboxy protégé,
un groupe N-(alkyl en C_1-C_6)-N-[(carboxy ou carboxy protégé) (alkyl en C_1-C_6)]carbamoyle,
un groupe (ar en C_6-C_{10})(alkyl en C_1-C_6)carbamoyle,
un groupe [(ar en C_6-C_{10})(alkyl en C_1-C_6) substitué par un groupe carboxy ou un groupe carboxy protégé] carbamoyle,
un groupe (cycloalkyl en C_3-C_7)carbamoyle,
un groupe N-[(cycloalkyl en C_3-C_7)(alkyl en C_1-C_6) substitué par un groupe carboxy ou un groupe carboxy protégé]carbamoyle,
un groupe (alkyl en C_1-C_6)sulfonylcarbamoyle, un groupe (aryl en C_6-C_{10})sulfonylcarbamoyle,
un groupe [(groupe hétéromonocyclique aromatique à 5 ou 6 chaînons) (alkyl en C_1-C_6) substitué par un groupe carboxy ou un groupe carboxy protégé]carbamoyle, dans lequel l'hétérocycle contient un à trois atomes d'azote,
un groupe (alkylène en C_3-C_{10})aminocarbonyle,
un groupe (alkylène en C_3-C_{10})aminocarbonyle substitué par un groupe carboxy ou un groupe carboxy protégé,
un groupe [(alkylène en C_3-C_{10})amino(alkyl en C_1-C_6)]carbamoyle substitué par un à deux substituant (s) choisi(s) parmi un groupe oxo, un groupe carboxy, un groupe carboxy protégé et un groupe carbamoyle,
un groupe morpholinocarbonyle,
un groupe (groupe hétéromonocyclique saturé à 5 ou 6 chaînons)carbamoyle, dans lequel l'hétérocycle contient un atome d'azote et un atome d'oxygène,
un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)carbamoyle, dans lequel l'hétérocycle contient un à trois atome(s) d'azote,
un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)carbamoyle, dans lequel l'hétérocycle contient un à deux atome(s) d'azote et un atome de soufre et peut être substitué par un groupe alkyle en C_1-C_6, un groupe (groupe hétérocyclique condensé au benzène à 9 ou 10 chaînons)carbamoyle, dans lequel l'hétérocyclique contient 1 à 2 atome(s) d'azote et un atome de soufre, un groupe (groupe hétéromonocyclique saturé à 5 ou 6 chaînons)(alkyl en C_1-C_6)carbamoyle, dans lequel l'hétérocycle contient un atome d'azote et un atome d'oxygène,
un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons)(alkyl en C_1-C_6)carbonyle, dans lequel l'hétérocycle contient 1 à 3 atome(s) d'azote, un groupe carbazoyle, un groupe di(alkyl en C_1-C_6) carbazoyle;
un groupe carboxy(alkyle en C_1-C_6); ou
un groupe (carboxy protégé)(alkyle en C_1-C_6); et

R^6 représente un atome d'hydrogène; ou
un groupe (groupe hétéromonocyclique aromatique à 5 ou 6 chaînons) (alkyle en C_1-C_6), dans lequel l'hétérocycle contient un à trois atome(s) d'azote.

6. Procédé selon la revendication 5, dans lequel :

R^1 représente un groupe carbamoyle;

un groupe alcanoyle en C_1-C_6;
un groupe amino(alcanoyle en C_1-C_6);
un groupe (alcoxy en C_1-C_6)carbonylamino(alcanoyle en C_1-C_6);
un groupe (cycloalkyl en C_3-C_7)uréido(alcanoyle en C_1-C_6);
un groupe (alcoxy en C_1-C_6)carbonyle;
un groupe (cycloalkyl en C_3-C_7)(alcanoyle en C_1-C_6);
un groupe (cycloalkyl en C_3-C_7)carbonyle;
un groupe (cycloalkyloxy en C_3-C_7)carbonyle;
un groupe benzoyle; un groupe naphtoyle;
un groupe phényl(alcanoyle en C_1-C_6); un groupe naphtyl(alcanoyle en C_1-C_6);

un groupe phényl(alcanoyle en C_1-C_6) substitué par un groupe amino;
un groupe phényl(alcanoyle en C_1-C_6) substitué par un groupe (alcoxy en C_1-C_6)carbonylamino;
un groupe halogénophényl(alcanoyle en C_1-C_6);
un groupe phényl(alcénoyle en C_2-C_6);
un groupe phénylglyoxyloyle;
un groupe phényl(alkyl en C_1-C_6)glyoxyloyle;
un groupe pyridylcarbonyle;
un groupe tétrahydropyridylcarbonyle;
un groupe tétrahydroquinolylcarbonyle;
un groupe tétrahydroisoquinolylcarbonyle;
un groupe morpholinylcarbonyle;
un groupe thiomorpholinylcarbonyle;
un groupe indolylcarbonyle;
un groupe pipérazinylcarbonyle substitué par un à trois substituant(s) choisi(s) parmi un groupe oxo et un groupe alkyle en C_1-C_6;
un groupe pyridyl(alcanoyle en C_1-C_6);
un groupe morpholinylcarbonyl(alcanoyle en C_1-C_6);
un groupe phényl(alkyl en C_1-C_6)sulfonyle;
un groupe N- ou N,N-di(alkyl en C_1-C_{10})carbamoyle;
un groupe hydroxy(alkyl en C_1-C_6)carbamoyle;
un groupe carboxy(alkyl en C_1-C_6)carbamoyle;
un groupe (alcoxy en C_1-C_6)carbonyl(alkyl en C_1-C_6)carbamoyle;
un groupe carbamoyl(alkyl en C_1-C_6)carbamoyle;
un groupe [N- ou N,N-di(alkyl en C_1-C_6)carbamoyl](alkyl en C_1-C_6)carbamoyle;
un groupe N-(alkyl en C_1-C_6)-N-[hydroxy(alkyl en C_1-C_6)]carbamoyle;
un groupe N-(alkyl en C_1-C_6)-N-[di(alkyl en C_1-C_6)carbamoyl(alkyl en C_1-C_6)]carbamoyle;
un groupe (alkylène en C_3-C_{10})aminocarbonyle;
un groupe di(alkyl en C_1-C_6)carbamoyl(alkylène en C_3-C_{10})aminocarbonyle;
un groupe N-(alkyl en C_1-C_6)-N-(cycloalkyl en C_3-C_7)carbamoyle;
un groupe mono- ou di-(cycloalkyl en C_3-C_7)carbamoyle;
un groupe [(cycloalkyl en C_3-C_7)substitué par un groupe hydroxy ou un groupe di(alkyl en C_1-C_6)carbamoyle ou un groupe di(alkyl en C_1-C_6)carbamoyl(alkyl en C_1-C_6)]carbamoyle;
un groupe (cycloalkyl en C_3-C_7)(alkyl en C_1-C_6)carbamoyle;
un groupe [(cycloalkyl en C_3-C_7)(alkyl en C_1-C_6) substitué par un groupe di(alkyl en C_1-C_6)carbamoyle] carbamoyle;
un groupe [phényl(alkyl en C_1-C_6) substitué par un groupe di (alkyl en C_1-C_6)carbamoyle]carbamoyle;
un groupe phénylcarbamoyle, dans lequel le groupe phényle peut être substitué par un à trois substituant (s) choisi(s) parmi un atome d'halogène, un groupe alkyle en C_1-C_6 et un groupe alcoxy en C_1-C_6;
un groupe pyridylcarbamoyle;
un groupe N-(alcoxy en C_1-C_6)carbonylpipéridylcarbamoyle;
un groupe morpholinyl(alkyl en C_1-C_6)carbamoyle;
un groupe (alcanoyl en C_1-C_6)carbazoyle;
un groupe (alkylène en C_3-C_{10})aminocarbamoyle;
un groupe N-(cycloalkyl en C_3-C_7)carbamoyl(alkyl en C_1-C_6)carbamoyle;
un groupe (alkylène en C_3-C_{10})aminocarbonyl(alkyl en C_1-C_6)carbamoyle;
un groupe pyridyl(alkyl en C_1-C_6)carbamoyle; ou
un groupe hexahydroazépinylcarbamoyle substitué par un groupe oxo;

R^2 représente un groupe alkyle en C_1-C_6;

R^3 représente un groupe indolyl(alkyle en C_1-C_6);

un groupe N-(alkyl en C_1-C_6)indolyl(alkyle en C_1-C_6); un groupe N-(alcanoyl en C_1-C_6)indolyl(alkyle en C_1-C_6);
un groupe phényl(alkyle en C_1-C_6); ou
un groupe naphtyl(alkyle en C_1-C_6);

R^4 représente un groupe alkyle en C_1-C_6;

un groupe amino(alkyle en C_1-C_6);
un groupe mono- ou di- ou tri-phényl(alcoxy en C_1-C_6)carbonylamino(alkyle en C_1-C_6);
un groupe carboxy(alkyle en C_1-C_6);
un groupe mono- ou di- ou tri-phényl(alcoxy en C_1-C_6)carbonyl(alkyle en C_1-C_6);
un groupe phényl(alkyle en C_1-C_6);
un groupe naphtyle(alkyle en C_1-C_6);
un groupe pyridyle(alkyle en C_1-C_6);
un groupe imidazolyl(alkyle en C_1-C_6); ou
un groupe thiazolyl(alkyle en C_1-C_6);

R^5 représente un groupe carboxy;

un groupe (alcoxy en C_1-C_6)carbonyle;
un groupe mono- ou di- ou tri-phényl(alcoxy en C_1-C_6)carbonyle;
un groupe benzoyl(alcoxy en C_1-C_6)carbonyle;
un groupe carbamoyle;
un groupe N- ou N,N-di(alkyl en C_1-C_6)carbamoyle;
un groupe (alkyl en C_1-C_6)carbamoyle substitué par un ou deux substituants choisis parmi un groupe carboxy, un groupe (alcoxy en C_1-C_6)carbonyle, un groupe mono- ou di- ou tri-phényl(alcoxy en C_1-C_6) carbonyle et un groupe benzoyl(alcoxy en C_1-C_6)carbonyle;
un groupe N-(alkyl en C_1-C_6)-N-[carboxy(ou(alcoxy en C_1-C_6)carbonyl)) (alkyl en C_1-C_6)]carbamoyle;
un groupe phényl(alkyl en C_1-C_6)carbamoyle;
un groupe [phényl(alkyl en C_1-C_6) substitué par un groupe carboxy ou un groupe (alcoxy en C_1-C_6) carbonyle]carbamoyle;
un groupe (cycloalkyl en C_3-C_7)carbamoyle;
un groupe [carboxy(cycloalkyl en C_3-C_7)(alkyl en C_1-C_6)]carbamoyle;
un groupe [(alcoxy en C_1-C_6)carbonyl(cycloalkyl en C_3-C_7)(alkyl en C_1-C_6)]carbamoyle;
un groupe (alkyl en C_1-C_6)sulfonylcarbamoyle;
un groupe phénylsulfonylcarbamoyle,
un groupe [pyridyl(alkyl en C_1-C_6) substitué par un groupe carboxy ou un groupe (alcoxy en C_1-C_6)carbonyl]carbamoyle;
un groupe (alkylène en C_3-C_{10})aminocarbonyle;
un groupe (alkylène en C_3-C_{10})aminocarbonyle substitué par un groupe carboxy ou un groupe (alcoxy en C_1-C_6)carbonyle;
un groupe [(alkylène en C_3-C_{10})amino(alkyl en C_1-C_6)]carbamoyle substitué par un à deux substituant (s) choisi(s) parmi un groupe oxo, un groupe carboxy, un groupe (alcoxy en C_1-C_6)carbonyle et un groupe carbamoyle;
un groupe morpholinocarbonyle;
un groupe morpholinylcarbamoyle;
un groupe pyridylcarbamoyle;
un groupe thiazolylcarbamoyle;
un groupe (alkyle en C_1-C_6)thiadiazolylcarbamoyle;
un groupe benzothiazolylcarbamoyle;
un groupe morpholinyl(alkyl en C_1-C_6)carbamoyle;
un groupe pyridyl(alkyl en C_1-C_6)carbamoyle;
un groupe carbazoyle,
un groupe di(alkyl en C_1-C_6)carbazoyle;
un groupe carboxy(alkyle en C_1-C_6);
un groupe (alcoxy en C_1-C_6)carbonyl(alkyle en C_1-C_6); ou
un groupe benzoyl(alcoxy en C_1-C_6)carbonyl(alkyle en C_1-C_6), et

R^6 et R^7représentent chacun un atome d'hydogène.

7. Procédé selon la revendication 6, dans lequel :

R^1 représente un groupe N- ou N,N-di(alkyl en C_1-C_{10})carbamoyle,
un groupe N-(alkyl en C_1-C_6)-N-(cycloalkyl en C_3-C_7)carbamoyle, un groupe N- ou N,N-di(cycloalkyl en C_3-C_7)carbamoyle, un groupe N-(alkyl en C_1-C_6)-N-[N,N-di(alkyl en C_1-C_6)carbamoyl(alkyl en C_1-C_6)]carbamoy-

le, un groupe phénylcarbamoyle, un groupe (alkylène en C_3-C_{10})aminocarbonyle ou un groupe N-(alkyl en C_1-C_6)-N-[hydroxy(alkyl en C_1-C_6)]carbamoyle,

R^2 représente un groupe alkyle en C_1-C_6,

R^3 représente un groupe indolyl(alkyle en C_1-C_6), un groupe N-(alcanoyl en C_1-C_6)indolyl(alkyle en C_1-C_6) ou un groupe N-(alkyl en C_1-C_6)indolyl(alkyle en C_1-C_6),

R^4 représente un groupe pyridyl(alkyle en C_1-C_6) ou phényl(alkyle en C_1-C_6),

R^5 représente un groupe carboxy,

un groupe (alcoxy en C_1-C_6)carbonyle,
un groupe carbamoyle ou
un groupe N- ou N,N-di(alkyl en C_1-C_6)carbamoyle, et

A représente un groupe méthylène ou un groupe -NH-.

8. Procédé selon la revendication 7, dans lequel :

R^1 représente un groupe isopropylcarbamoyle, un groupe 2-méthylbutylcarbamoyle, un groupe heptylcarbamoyle, un groupe diméthylcarbamoyle, un groupe diéthylcarbamoyle, un groupe dipropylcarbamoyle, un groupe diisopropylcarbamoyle, un groupe dibutylcarbamoyle, un groupe diisobutylcarbamoyle, un groupe pyrrolidin-1-ylcarbonyle, un groupe pipéridin-1-ylcarbonyle, un groupe 3,5- ou 2,6-diméthylpipéridin-1-ylcarbonyle, un groupe hexahydro-1H-azépin-1-ylcarbonyle ou un groupe octahydroazocin-1-ylcarbonyle,

R^2 représente un groupe isobutyle,

R^3 représente un groupe indol-3-ylméthyle, un groupe N-formylindol-3-ylméthyle, un groupe N-méthylindol-3-ylméthyle, un groupe N-éthylindol-3-ylméthyle, un groupe N-propylindol-3-ylméthyl ou un groupe N-isobutylindol-3-yl-méthyle,

R^4 représente un groupe 2-pyridylméthyle ou benzyle,

R^5 représente un groupe carboxy, un groupe méthoxycarbonyle, un groupe éthoxycarbonyle, un groupe carbamoyle, un groupe méthylcarbamoyle, un groupe éthylcarbamoyle, un groupe propylcarbamoyle, un groupe isopropylcarbamoyle, un groupe butylcarbamoyle, un groupe N,N-diméthylcarbamoyle ou un groupe N,N-diéthylcarbamoyle.

9. Modification du procédé défini dans l'une quelconque des revendications 1 à 8, comprenant en outre l'étape consistant à mélanger et à présenter le composé obtenu conformément au procédé de l'une quelconque des revendications 1 à 8 ou un sel pharmaceutiquement acceptable de celui-ci avec un véhicule ou un excipient pharmaceutiquement acceptable.